ISSN 1305 - 4953
e-ISSN 2587 - 1579

OSMANGAZİ TIP DERGİSİ

Osmangazi Journal of Medicine

Cilt/Vol 47 Sayı/Issue 1 Jenuary/Ocak 2025

Eskişehir Osmangazi University Publications

OSMANGAZİ TIP DERGİSİ
OSMANGAZI JOURNAL OF MEDICINE

Danışma Kurulu

Yazarları Bilgilendirme

Osmangazi Tıp Dergisi, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi'nin resmi yayın organıdır. Klinik ve deneysel çalışmalar, olgu sunumları, derlemeler, editöre mektup ve tıp alanında klinik haber olmak üzere hakemli ve açık erişimli bir dergidir. Dergi Ocak, Nisan, Temmuz ve Ekim aylarında olmak üzere yılda dört kez çıkarılır.
Derginin dili Türkçe/İngilizce dir. Yazıların dergide yer alabilmesi için daha önce başka bir dergide yayınlanmamış olması ve yayınlanmak üzere gönderilmemiş olması gerekmektedir.

Makalelerin formatı VANCOUVER Reference Style Guide kurallarına göre düzenlenmelidir (https:// http://openjournals.net/files/Ref/VANCOUVER%20Reference%20guide.pdf).
Sunulan yazı öncelikle yayın kurulu tarafından kabul veya reddedilir. Kabul edilen yazılar yayın kurulu tarafından belirlenen çift-kör, bağımsız ve önyargısız hakemlik (peer-review) ilkelerine göre en az iki hakem tarafından değerlendirilir. Son karar dergi Yayın Kurulu'nundur. Yayın Kurulu'nda derginin inceleme aşamaları:

1- Editör sekreteri tarafından teknik inceleme (benzerliklerin denetlenmesi)
2- Baş Editör tarafından inceleme: [reddetmek ya da yayını ilerletme değerlendirmesi],
3- Bölüm Editörü tarafından inceleme,
4- Haftalık Yayın Kurulu Toplantısında Değerlendirme [reddetmek ya da yayını ilerletme değerlendirmesi],
5- İki ya da daha fazla hakem tarafından inceleme,
6- Bölüm Editörü tarafından değerlendirilme,
7- Haftalık Yayın Kurulu Toplantısında Değerlendirme [reddetmek veya kabul etmek],
8- Taslak hazırlama
9- DOI numarası atama ve
10- Yayınlama aşaması

olmak üzere 10 adımdan oluşmaktadır.

Yazılar bir başvuru mektubu ile gönderilmeli ve bu mektubun sonunda tüm yazarların imzası bulunmalıdır. Yazıların sorumluluğu yazarlara aittir. Tüm yazarlar bilimsel katkı ve sorumluluklarını ve çıkar çatışması olmadığını bildiren toplu imza ile yayına katılmalıdır. Araştırmalara yapılan kısmi de olsa nakdi ya da ayni yardımların hangi kurum, kuruluş, ilaç-gereç firmalarınca yapıldığı dipnot olarak bildirilmelidir. Yazı kabul edildiği takdirde bütün basım, yayım ve dağıtım hakları (copyright) Osmangazi Tıp Dergisine devredilmiş olur.

Etik
Osmangazi Tıp Dergisinde yayınlanmak amacıyla gönderilen deneysel, klinik ve ilaç araştırmaları için etik kurul onay raporu gereklidir. Bakınız: (http://uvt.ulakbim.gov.tr/tip/icmje_08.pdf).
(Sayfa 5-6, 8-9).

Yazım Kuralları
Orjinal makaleler en fazla 3000; derlemeler en fazla 4000 kelime olmalı; olgu sunumları ise 1600 kelimeyi geçmemelidir.

Yazılar; A4 kağıdı boyutuna uygun olarak, sayfanın her iki kenarında yaklaşık üçer santim boşluk bırakılacak şekilde 1,5 satır aralığı ile Times New Roman yazı tipinde yazılmalı ve 12 font büyüklüğünde olmalıdır.

Orijinal Makaleler, Başlık sayfası, Yazar(lar), Türkçe/İngilizce Özet, Anahtar kelimeler, Giriş, Gereç ve Yöntem, Bulgular ve Analizler, Tartışma ve Sonuç, Teşekkür, Kaynaklar ve Ekler bölümlerinden
oluşmalıdır.

Olgu bildirimi, Başlık sayfası, Yazar(lar), Türkçe/İngilizce Özet, Anahtar kelimeler, Giriş, Olgu Bildirisi, Tartışma ve Sonuç, Kaynaklar ve Ekler bölümlerinden oluşmalıdır.

Editöre mektup, son bir yıl içinde dergide yayımlanan makaleler ile ilgili ya da bir makale ile ilişkisi olmayan ancak kişinin bilgi ve deneyimlerini aktarmak amacıyla yazılmış en fazla 1000 kelimelik yazılardır. En fazla iki yazar tarafından hazırlanır ve 10 kaynağı aşmamalıdır.

Başlık Sayfası
Bilimsel yazının başlığı, Türkçe ve İngilizce olarak sadece ilk harf büyük olacak şekilde alt alta yazılmalı ve tek ya da iki satırlık bir isim olmalıdır.

Yazar(lar)
Başlık sayfasının hemen altına yazarların açık olarak adı-soyadı, ünvanları, çalıştıkları kurum ile çalışmanın yapıldığı kurum belirtilmelidir. İletişim kurulacak yazarın posta adresi ile telefon numarası ve e-posta adresleri yazılmalıdır. Ayrıca derginin ön yüzünde kullanılmak üzere Türkçe ve İngilizce kısa başlık yazılmalıdır.

Özet
Başlık sayfasından sonra ayrı bir sayfada araştırma ve derlemeler için en az 200, en fazla 250, olgu bildirileri için en az 100, en fazla 150 kelimeden oluşan bir özet bulunmalıdır.
Araştırma Makaleleri için yazılacak özet amaç, gereç ve yöntem, bulgular, sonuç olmak üzere yazılmalıdır. Türkçe özetin altında aynı düzende yazılmış İngilizce özet yer almalıdır.

Anahtar Kelimeler
Türkçe ve İngilizce özetlerin hemen altında en az 4 anahtar kelime verilmelidir.

Şekil ve Fotoğraflar
Fotoğraf ve şekiller ayrı bir dosya halinde gönderilmelidir. Şekillerin alt yazıları ayrı bir dosyaya, şekil numarası bildirilerek yazılmalı ve şekil numaraları metin içinde mutlaka

belirtilmelidir. Mikroskopik resimlerde büyütülme oranı ve boyama tekniği açıklanmalıdır. Resim, şekil, grafik ve tabloların çözünürlükleri en az 300 dpi olmalıdır. Yazar başka kaynaktan aldığı resim, şekil, grafik ve tablolar için telif hakkı sahibi kişi ve kuruluşlardan izin almalı ve yazı içinde bunu belirtmelidir. Yazı içinde ilaçların veya aletlerin özel isimleri kullanılamaz.

Tablolar
Ayrı bir dosyaya çift aralıklı olarak yazılmalı, tablo içinde enine ve boyuna bölme çizgileri kullanılmamalıdır. Her tablonun üzerine numara ve başlık yazılmalıdır. Tablo numaraları metin içinde mutlaka kullanılmalıdır.

Kaynaklar
Kaynaklar yazıda geçiş sırasına göre numaralandırılmalıdır. Dergi isimleri Index Medicus'a uygun olarak kısaltılmalıdır. Bakınız:
http://openjournals.net/files/Ref/VANCOUVER%20Reference%20guide.pdf

Örnekler:
Tek yazarlı kitap:
Yazar Soyadı, adı baş harfi. (Yıl). Kitap adı (italik yazılacak). Yayın yeri: Yayınevi/ Matbaa adı.
Comfort A. A good age. London: Mitchell Beazley; 1997.
Çok yazarlı kitap:
Birinci yazar soyadı ve adının baş harfi. 2. yazar soyadı ve adının baş harfi. …, 7.ci yazar soyadı ve adının baş harfi. (Yıl). Kitap adı (italik yazılacak).
Yayın yeri: Yayınevi/matbaa adı.

- Madden R, Hogan T. The definition of disability in Australia: Moving towards national consistency. Canberra: Australian Institute of Health and Welfare; 1997.

Sadece elektronik basılı kitap:

- Reid DB. Australasian association of doctors' health advisory services. Med J Australia [serial online]. 2005 [cited 2006 Mar 28];182(5):255. Available from: Health and Medical Complete.

Tek yazarlı makale:
Yazar soyadı, adının baş harfi. (Yıl). Makale başlığı, dergi adı (italik yazılacak), cilt(sayı), başlangıç sayfason sayfa.

- Wharton N. Health and safety in outdoor activity centres. J Adventure Ed Outdoor Lead. 1996;12(4):8–9.

Çok Yazarlı Makale: Yazar sayısı 6 ve üstünde ise ilk 3 yazar yazıldıktan sonra et al ifadesi eklenmelidir.

- Wharton N. Health and safety in outdoor activity centres. J Adventure Ed Outdoor Lead. 1996;12(4):8–9.

Bildiriler, Konferans Notları
Chasman J, Kaplan RF. The effects of occupation on preserved cognitive functioning in dementia. Poster session presented at: Excellence in clinical practice, 4th Annual Conference of the American Academy of Clinical Neuropsychology; 2006 Jun 15–17; Philadelphia, PA.

İletişim
Editör Sekreteri:
Yeşim ÇELİKKANAT
Adres: Osmangazi Tıp Dergisi, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, 26480 Eskişehir, Türkiye
Tel: +90 222 239 29 79 / 4489
Fax: +90 222 239 37 72
e-Posta: otd@ogu.edu.tr

Dergi web sayfası:
http://dergipark.gov.tr/otd/

Basımevi
Eskişehir Osmangazi Üniversitesi Basımevi
Adres: Eskişehir Osmangazi Üniversitesi Meşelik Yerleşkesi, Eskişehir
Tel: +90 222 239 37 50 / 3105
Fax: +90 222 229 30 47
e-mail: esogugrafik@gmail.com

OSMANGAZİ TIP DERGİSİ / OSMANGAZİ JOURNAL OF MEDICINE

ULAKBİM TR Dizin (https://cabim.ulakbim.gov.tr/tr-dizin/tr-dizinde-dizinlenen-dergi-listesi/)

OpenAİRE (https://explore.openaire.eu)

DRJI (http://olddrji.lbp.world)

Türk Medline (http://www.turkmedline.net/degilistesi.php?journal=348)

Google Scholar (https://scholar.google.com.tr/)

BASE (https://www.base-search.net)

tarafından indekslenmektedir.

Osmangazi Journal of Med, 2025;47(1): 1-7
DOI: 10.20515/otd. 1491680

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Association Between IFN-λ4 rs12979860 And rs11322783 Polymorphisms with Spontaneous Clearance In Chronic Hepatitis B

Kronik Hepatit B'de IFN-λ4 rs12979860 ve rs11322783 Polimorfizmlerinin Spontan Klirens ile İlişkisi

[1]Fariz Emrah Özkan, [2]Semih Dalkılıç, [2]Lütfiye Dalkılıç , [3]Abdurrahman Şahin, [3] İbrahim Halil Bahçecioğlu, [3]Mehmet Yalnız

[1]Department of Internal Medicine, Medicine Faculty, Firat University, Elazig, Türkiye
[2]Molecular Biology and Genetics, Department of Biology, Faculty of Science, Firat University, Elazig, Türkiye
[3]Department of Gastroenterology, Medicine Faculty, Firat University, Elazig, Türkiye

ORCID ID of the authors
FEÖ. 0000-0002-4347-0366
SD. 0000-0002-6892-247X
LKD. 0000-0002-6791-3811
AŞ. 0000-0001-5477-9492
İHB. 0000-0001-9705-8281
MY. 0000-0001-7776-4154

Correspondence / Sorumlu yazar:
Fariz Emrah ÖZKAN
Department of Internal Medicine, Medicine Faculty, Firat University, Elazig, Türkiye
e-mail: dr.emrah.oz@gmail.com

Ethics Committee Approval: This study was designed and conducted in accordance with the ethical guidelines set forth in the Declaration of Helsinki, and the study protocol was approved by the Fırat University Non-interventional Clinical Researches Ethics Committee (Date: 19.07.2018, Decision No:13/05).

Informed Consent: This study did not require informed consent.

Authorship Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Copyright Transfer Form: Copyright Transfer Formwas signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This research was supported by the Firat University Scientific Research Project Office (project number: TF.18.51).

Abstract: Many studies have been published on the association between IFN-λ3 and IFN-λ4 polymorphisms and treatment related or spontaneous clearance of chronic hepatitis C. To date there is little known about the impact of IFN-λ4 polymorphisms on the natural history of chronic hepatitis B(CHB). This study aimed to investigate the role of IFN-λ4 polymorphisms on the course of CHB and to influence the presence of spontaneous clearance (SC) in CHB patients. One hundred and twenty-two patients who had CHB, and 81 subjects who had spontaneous resolution of HBV were analyzed regarding IFN-λ4 rs12979860 and rs11322783 single-nucleotide polymorphisms. We couldn't found any significant difference between CHB groups and SC groups in terms of IFN-λ4 rs12979860 polymorphisms and, the CC, C/T and TT genotypes represented 49%, 45% and 5% of CHB patients and, %46, 43% and 11% of SC group respectively (p=0.65). On the other hand, in IFN-λ4 rs11322783 polymorphisms analysis, recessive G/G allele was more common in SC group compared to CHB group (5% vs 16%, p=0.04; OR: 3,55). Moreover, non-G/G genotypes had significantly higher in CHB patients compared to SC group (95% vs 84%, p=0.013; OR:3.55). Our results suggest that IFN-λ4 rs11322783 polymorphism may be a predictor of spontaneous clearance in HBV infected patients. The role of IFN-λ4 polymorphisms needs to be investigated in the natural history of HBV.
Keywords: Interferon-λ4, Hepatitis B virus, Single nucleotide polymorphism, Spontaneous clearance

Özet: IFN-λ3 ve IFN-λ4 polimorfizmleri ile kronik hepatit C'nin tedaviye bağlı veya spontan klirensi arasındaki ilişki hakkında birçok çalışma yayınlanmıştır. Bugüne kadar IFN-λ4 polimorfizmlerinin kronik hepatit B'nin (KHB) doğal seyri üzerindeki etkisi hakkında çok az şey bilinmektedir. Bu çalışma, IFN-λ4 polimorfizmlerinin KHB'nin seyri üzerindeki rolünü ve KHB hastalarında spontan klirens (SK) mevcudiyeti üzerine etkisini araştırmayı amaçlamıştır. Yüz yirmi iki KHB hastası ve spontan HBV rezolüsyonu olan 81 birey IFN-λ4 rs12979860 ve rs11322783 tek nükleotid polimorfizmleri açısından analiz edilmiştir. IFN-λ4 rs12979860 polimorfizmleri açısından KHB ve SK grupları arasında anlamlı bir fark bulunamamış olup, CC, C/T ve TT genotipleri sırasıyla KHB hastalarının %49, %45 ve %5'ini, SK grubunun ise %46, %43 ve %11'ini temsil etmiştir (p=0.65). Öte yandan, IFN-λ4 rs11322783 polimorfizm analizinde, resesif G/G alleli KHB grubuna kıyasla SK grubunda daha sıktı (%5'e karşı %16, p=0,04; OR: 3,55). Ayrıca, G/G olmayan genotipler KHB hastalarında SK grubuna kıyasla anlamlı derecede daha yüksekti (%95'e karşı %84, p=0,013; OR:3,55). Sonuçlarımız, IFN-λ4 rs11322783 polimorfizminin HBV ile enfekte hastalarda spontan klirensin bir belirleyicisi olabileceğini düşündürmektedir. IFN-λ4 polimorfizmlerinin HBV'nin doğal seyrindeki rolünün araştırılması gerekmektedir.
Anahtar Kelimeler: İnterferon-λ4, Hepatit B virüsü, Tek nükleotid polimorfizmi, Spontan klirens

Received 31.05.2024
Accepted : 31.10.2024
Published : 06.11.2024

How to cite/ Atıf için: Ozkan FE, Dalkilic S, Dalkilic L , Sahin A, Bahcecioglu IH, Yalniz M, Association Between IFN-λ4 rs12979860 And rs11322783 Polymorphisms With Spontaneous Clearance In Chronic Hepatitis B, Osmangazi Journal of Medicine, 2025;47(1): 1-7

1. Introduction

Hepatitis B virus is a virus that affects more than 350 million people and causes health problems such as cirrhosis, hepatocellular carcinoma, chronic hepatitis and approximately 1 million deaths per year. It is thought that 2 billion people worldwide have encountered this virus and close to 400 million people are chronically infected with HBV (1).

Patients with infectious diseases often show heterogeneous clinical courses associated with a range of morbidities and variable mortality. This is due to a number of factors that encompass complex aspects of host-pathogen interactions. Interferons play an important role in these interactions that determine the outcome of many viral, bacterial, fungal and parasitic infections (2, 3).

Interferon-lambdas (IFN-λs) modulate immunity through a network of genes induced in infections and autoimmune diseases. IFN-λs act by binding to the heterodimeric IFN-λ receptor (IFN-λR), which activates the STAT phosphorylation-dependent signal cascade. Thus, hundreds of IFN-stimulated genes are induced and this complex modulates various immune functions via feed-forward and feedback loops.

The genetic variations in the form of a series of single-nucleotide polymorphisms (SNPs) associated with genes involved in the IFN-λ signaling cascade have been identified, and these single-nucleotide polymorphisms have been associated with the clinical course and treatment outcomes of hepatitis B and C virus infection (4). In the past decade, it was demonstrated that homozygous carriage of the C allele in rs12979860 of IFN-λ3 gene on chromosome 19 (also known as IL28B polymorphism) substantially increases the likelihood of spontaneous clearance of acute HCV infection, and also improves outcome of interferon-based HCV therapy. After the widespread use of direct acting antiviral agents (DAA) for HCV treatment, the clinical relevance of the IFN- -λ3 polymorphism decreased.

IFN-λ4 is the most divergent member of the IFN- λ family and has only 29% amino acid identity with IFN- λ3, unlike the >80% homology observed between IFN- λ1, IFN- λ2 and IFN-λ3 (5). Several studies demonstrated that several IFN-λ4 better outcomes for the clearance of chronic HCV (5-7). Beside the association of IFN-λ gene polymorphisms with the immune response, disease progression and hepatocellular carcinoma in patients with HBV infection, IFN-λ gene polymorphisms also affect the spontaneous viral clearance rate of HBV patients through interaction with other genes (8). There are insufficient data about the influence of IFN-λ4 polymorphisms on treatment related or spontaneous clearance of HBV infection (9, 10).

In the current study, we aimed to investigate the effect of IFN-λ4 rs12979860 and rs11322783 polymorphisms on the spontaneous clearance of HBV among subjects infected with HBV and subjects who had spontaneous HBV seroclearance.

2. Materials and Methods

2.1. Study Population

This study included a total of 214 subjects who applied to the Gastroenterology Clinic xxx Medicine Faculty between August 2018 and March 2019. One hundred and twenty-two of them had chronic hepatitis B (CHB) infection and 81 subjects had spontaneous clearance for HBV. All subjects in CHB group were seropositive for HBsAg for at least 6 months, and 80% of them on therapy with nucleoside/nucleotide analogues(NA). These patients had elevated serum alanine aminotransferase (ALT) levels and serum HBV DNA levels before therapy. Subjects who had seronegative results for HBsAg in combination with seropositive results for anti-HBs and/or anti-HBc IgG were recruited to spontaneous clearance group for HBV (SC). Individuals under the age of 18, pregnant women and individuals who did not want to participate in the study were excluded. Patients co-infected with hepatitis C virus and/ hepatitis D virus were also excluded.

Serum samples were tested for HBsAg, anti-HBs, anti-HBc IgG, HBeAg, Anti-HBe and anti-HCV with macro enzyme-linked immunosorbent assay (ELISA) using Abbott Architect kits in the Abbott Architect i2000 SR system (Abbott, Axsym, Ireland) according to the manufacturer's instructions. The presence of anti-HDV was analyzed using micro-ELISA (HDV Ab, Enzyme Immunoassay Test Kit, Delta Biologicals, Italy) with the Triturus system (Triturus, Grifols, Spain) according to the manufacturer's instructions. A 5 ml blood samples taken from the study participitans at the time of admission were collected into tubes with ethylenediaminetetraacetic acid (EDTA) and stored at -80 degrees, and polymorphisms were studied from these blood.

2.2.Molecular analysis

DNA isolation protocol

DNA of the patients was extracted using Invitrogen Purelink Genomic DNA extraction kit (Thermo Fischer Scientific, Wilmington, DE, USA) with the following the manufacturer's protocol. Quality control and quantity measurements of the isolated genomic DNA samples were performed by Qubit Fluorometer protocol as recommended by the manufacturers (Thermo Fischer Scientific, Wilmington, DE, USA).

SNP Genotyping

IFN-λ4 (rs12979860) and IFN-λ4 (rs11322783) genotyping was performed by TaqMan technology (Thermo Fisher Scientific) in a StepOne Plus Real Time PCR System (Applied Biosystems, Foster City, CA). SNP and allele (genotype) calling was carried out by a standard end-point analysis with the aid of commercial genotype-calling software (TaqMan™ Genotyper Software v1.0.1).

2.3. Statistical analysis

Statistical analyzes were performed using the SPSS (Statistical Program for Social Sciences) version 22 software. Results were presented as numbers (percentage) for categorical variables, mean ± standard deviation for normally distributed continuous variables, and median ± interquantil range (IQR) for non-normally distributed variables. Chi-square and Fisher's exact test were used to compare group ratios. While Student's t test was used for normally distributed variables, Mann-Whitney U and Wilcoxon sign tests were used for non-normally distributed variables to compare group means. Odd ratio (OR) and confidence interval(CI) were used to evaluate the relationship for IFN--λ4 polymorphism alleles between the CHB group and the spontaneous clearance group. Odd ratio and CI were calculated with logistic regression analysis and Hardy-Weinberg equilibrium using SNPStat program. P< 0.05 was considered statistically significant.

2.4. Figures

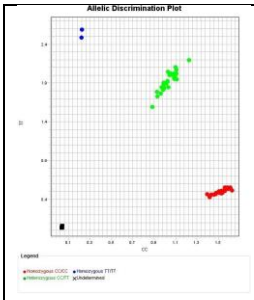


Figure 1. Allelic discrimination plot for IFN-λ4 (rs12979860) polymorphism

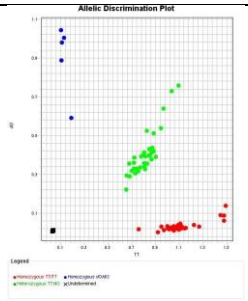


Figure 2. Allelic discrimination plot for IFN-λ4 (rs11322783) polymorphism

2.5. Tables

Table 1. Demographic, serological and laboratory parameters of CHB group and SC group

	CHB group (n=122)	**SC group (n=92)**	**P**
Age	47.1±12.6	66.2±14.2	**<0.01**
Gender, male (%)	69 (56)	51 (55)	0,87
NA tratment, n(%)	98 (80)	-	
IFN α/ PegIFN α	-	-	
Lamuvidine	6 (6)	-	
Telbivudine	5 (5)	-	
Entecavir	31 (32)	-	
Tenofovir	56 (57)	-	
HBeAg, n (%)	17 (14)	-	
Anti-HBe, n (%)	94 (77)	-	

White blood cell count	6320 ± 2530	6525 ± 2945	0.45
Hemoglobin	14.3 ± 2.7	11.9 ± 2.4	**<0.01**
Platelet count	237000 ± 75000	225000 ± 147000	0.87
ALT	21 ± 14	22.5 ± 29	0.81
AST	22 ± 12	25.5 ± 23	0.08
GGT	16 ± 19	48 ± 111	**<0.01**
ALP	73 ± 32	81.5 ± 71	**<0.01**
LDH	198 ± 42	212 ± 110	**<0.01**
Protein	7.3±0.6	6.4±1.1	**<0.01**
Albumin	4.3±0.4	3.6±0.6	**<0.01**
BUN	29 ± 10	34 ± 24	**<0.01**
Creatinin	0.76 ± 0.26	0.76 ±0.37	0.71
INR	1.0±0.1	1.1±0.2	**<0.01**
aPTT	23±7	26 ± 5	**<0.01**

Table 2. Comparison of IFN-λ4 rs12979860 polymorphism analysis of CHB and SC groups

Genotype	**CHB group (%) (N=128)**	**SC group (%) (N=81)**	**p**	**OR (95% CI)**
C/C	63 (49%)	37 (46%)		1.00
C/T	58 (45%)	35 (43%)	0.65	1.09 (0.60-1.97)
T/T	7 (5%)	9 (11%)		1.59 (0.49 -5.10)
C	184 (72%)	109 (67%)		
T	72 (28%)	53 (33%)		

Table 3. Comparison of IFN-λ4 rs11322783 polymorphism analysis of of CHB and SC groups

Genotype	**CHB group (%) (N=128)**	**SC group (%) (N=81)**	**p**	**OR (95% CI)**
T/T	63 (49%)	33 (41%)		1.00
T/D	58 (45%)	35 (43%)		1.15 (0.64 -2.09)
G/N	7 (5%)	13 (16%)	**0.04**	3.55 (1.29-9.74)
T/T - T/G	121 (95%)	68 (84%)	**0.01**	1.00
G/N	7 (5%)	13 (16%)		3.30 (1.26-8.68)
T	184 (72%)	101 (62%)		
G	72 (28%)	61 (38%)		

3. Results

A total of 214 patients, 92 in CHB group and 122 in SC group, were recruited to this study. Sixty-nine of patients (56%) in CHB group and 51 subjects (55%) in SC group were male (p>0.05). Patients in CHB group were older then in SC group (66.2±14.2 years vs 47.1±12.6 years; p<0,01). Fourteen patients (17%) in CHB group were HBeAg positive. Ninety-eight patients in CHB group were on treatment with NA. Six of them were on Lamuvidine (6%), five (5%) on Telbivudine, 31 (32%) on Entecavir, and 56 (57%) on Tenefovir disoproxil fumarate treatments. Demographic, serological and laboratory parameters of two groups were given in Table 1.

3.1. Analysis of IFN-λ4 rs12979860 and rs11322783 single-nucleotide polymorphisms

Allelic discrimination plot for IFN-λ4 rs12979860 polymorphism was given in Figure 1. No significant difference was found between the groups in the comparison of the allele and genotype frequency of IFN-λ4 rs12979860 in chronic HBV patients and HBV-experienced groups during DNA extraction for interferon lambda four rs12979860 polymorphism analysis (p=0.65) (Table 2).

Allelic discrimination plot for IFN-λ4 rs 1322783 polymorphism was given in Figure 2. Comparing the allele and genotype frequency of IFN-λ4 rs12979860 in the DNA extraction stage for interferon lambda four rs11322783 polymorphism analysis, it was found that the G/G allele was more common in SC group than in chronic HBV patients (p=0.04; OR: 3,55 (1,29-9,74) (Table 3). In the evaluation of co-dominant alleles by combining them, it was observed that the recessive allele was more frequent in the similarly SC group than in the group with chronic HBV [p=0.013; OR: 3.55 (1.29-9.74) 3.30 (1.26-8.68)] (Table 3).

4. Discussion

Interferon λs modulate immunity through a network of genes induced in infections and autoimmune diseases. STAT acts by binding to the heterodimeric IFN-λR, which activates the phosphorylation-dependent signal cascade. Thus, hundreds of IFN-stimulated genes are induced and this complex modulates various immune functions via feed-forward and feedback loops (2).

Expression of interferon λ ligands is modulated by SNPs in both transcription factor binding sites and methylation sites of the promoter region, as well as frameshift mutations. The dual role of interferon lambdas, their direct antiviral effects and longer-lasting immunomodulatory effects on T and B cell activation and modulation, may lead to possible multiple interactions with different types of infectious diseases. IFNs protect cells against viral infections. On top of that, each virus has developed specific ways to inhibit IFN signaling and its effects (11). Although these results from mouse studies are very important, a number of important differences from human results have also been noted. In a human chimeric mouse model using human hepatocytes, the response rates of human and mouse hepatocytes to IFN-λ were found to be quite different, and especially in mice, hepatocytes did not respond to IFN-λ (12). Also, the expression of IFN-λR in immune cells appears to be strikingly different. B-cells in humans were responsive to IFN-λs, whereas B-cells in mice were unresponsive to IFN-λs (13).

The clinical impact of SNPs at the IFN-λ3/4 locus was initially observed in the context of IFN-α therapy outcomes in patients with chronic HCV. Most studies have concluded that the minor alleles of the SNPs rs12979860 (CT/TT) and rs8099917 (TG/GG) are associated with reduced IFN-λ3 expression observed in serum in liver biopsies during chronic HCV infection. However, the TT allele of rs12979860 in hepatocytes has also been shown to express higher levels of IFN- λ1 and IFN-λ3(14). Although the rs12979860 SNPs have been specifically associated with IFN- λ3/λ4 expression, these SNPs may also affect the expression of other IFN-λ genes (15). In a study examining the effect of IFN-λ4 rs12979860 polymorphism on HCV-related diseases, it was found that HCV-related diseases were more common in individuals with C/T or T/T genotype (16).

Recently, several studies were also evaluated several IFN-λ4 polymorphisms on Sars-cov-2. In one study conducted by Mohlenberg et al., the effect of IFN-λ4 polymorphism on immune response was investigated in individuals infected with Sars-cov-2, and no significant difference was found between significant groups (15). Likewise, results of another study on individuals infected with Covid-19 showed that the rate of infection was higher in individuals carrying the IFN-λ4 rs12979680 polymorphism (16).

In this study, it was aimed to determine whether IFN-λ4 rs12979860 and rs11322783 polymorphisms have a role on the clearance of chronic HBV infection. In the literature, only two studies

evaluated IFN-λ4 polymorphisms in HBV infection. In a retrospective study, Limothai et al. investigated IFN-λ4 ss469415590 polymorphism in 254 CHB patients that treated with PEGIFN for 48 weeks, and showed that there was no relationship between IFN-λ4 ss469415590 polymorphism and treatment response (9). Another study investigated IFNL4rs368234815, rs12971396, rs12979860, and rs8099917 polymorphisms among patients with CHB and those had seroclearance for HBV. They found that none of these IFN polymorphisms related with clearance of virus (10). Our results were compatible with the results of mentioned study. We also couldn't detect any difference in terms of IFN-λ4 rs12979860 polymorphism between CHB group and SC group.

On the other hand, in the rs11322783 polymorphism analysis, when the allele and genotype frequencies were compared between the groups, we found that the G/G allele was more common in SC group compared to CHB group. In the evaluation of co-dominant alleles by combining them, it was seen that the recessive allele was more common in the similarly passed group than in the group with chronic HBV. To our knowledge, this is the first study evaluating IFN-λ4 rs11322783 polymorphism in HBV. While individuals carrying IFN-λ4-TT allele of the rs11322783 polymorphism show aborted expression of IFN-λ4 protein, IFN-λ4-ΔG polymorphism can synthesize the full-length functional IFN-λ4 protein (17). According to the current knowledge, IFN-λ4 is produced and secreted in response to viral infections, at relatively low levels and compared to other IFN-λs. IFN-λ4 is a more potent and locally acting IFN λ form (18). Full-length production of IFN-λ4 protein among patients carrying IFN λ4-ΔG allele may result in higher production of this more potent IFN and, thus increasing possibility of spontaneous clearance of viral infections like HBV. Today, studies on polymorphisms are ongoing.

In a study, it was shown that PEG-IFN activity was higher in patients with genetic variations in IL28B and HbeAg positive CHB patients (19). In another study, HbsAg seroclerance rate was found to be higher in young patients diagnosed with CHB infection with HLA-DP and IL28B genetic mutations (20). IFNL4 rs12979860 showed a significant increase in HBV DNA loads in patients with the CC genotype compared to patients with the CT and TT genotypes. However, no consistent relationship was found between the IFNL4 rs12979860 polymorphism and the outcome of HBV infection (21). One of the most fatal outcomes of CHB infection is the development of HCC. There are many developments on this subject in global studies. In a study, no significant difference was observed between polymorphisms in the IL28B gene and the development of HCC (22). In another study conducted on IL28B, while no activity was found regarding the immune response in patients diagnosed with CHB and HIV, it was observed that the polymorphism was effective in the response to treatment in patients diagnosed with HCV (23).

Limitations

There are several limitations in the current study, which must be addressed. Our study is a single center study which included in a small number of patients and, thus our results are not sufficient to comment on IFN-λ4 polymorphisms in the natural history of chronic HBV infection. Secondly, we were unable to verify our findings using another independent population and, our results cannot be generalized to the whole population. Moreover, the significant diversity in IFNs and multiple SNPs poses a complexity problem that is difficult to address.

5. Conclusion

In conclusion, it is increasingly recognized that IFN-λs and their modulation by SNPs are factors that play important roles in a wide range of infectious diseases. Though most of the studies in the literature about IFN-λs are mostly on HCV. In this study, the incidence of IFN-λ4 rs11322783 and rs12979860 polymorphisms in patients with CHB and those had spontaneous clearance for HBV were investigated. The IFN-λ4-ΔG allele of rs11322783 polymorphism was found to be more common in spontaneous clearance group. Using IFN-λ4 rs11322783 SNP may guide us to predict the more probable group of spontaneous clearance among CHB patients. These findings need to be confirmed in larger groups of patients with CHB.

REFERENCES

1. Lee WM. Hepatitis B virus infection. N Engl J Med. 1997;337(24):1733-45.
2. Syedbasha M, Egli A. Interferon Lambda: Modulating Immunity in Infectious Diseases. Front Immunol. 2017;8:119.

3. Coomes SM, Pelly VS, Kannan Y, Okoye IS, Czieso S, Entwistle LJ, et al. IFNgamma and IL-12 Restrict Th2 Responses during Helminth/Plasmodium Co-Infection and Promote IFNgamma from Th2 Cells. PLoS Pathog. 2015;11(7):e1004994.
4. Liu B, McGilvray I, Chen L. IFN-lambda: A New Class of Interferon with Distinct Functions-Implications for Hepatitis C Virus Research. Gastroenterol Res Pract. 2015;2015:796461.
5. Waldenstrom J, Hellstrand K, Westin J, Nilsson S, Christensen P, Farkkila M, et al. Presence of interferon-lambda 4, male gender, absent/mild steatosis and low viral load augment antibody levels to hepatitis C virus. Scand J Gastroenterol. 2021;56(7):849-54.
6. Xie X, Zhang L, Chen YZ. Association between IFNL4 rs368234815 polymorphism and sustained virological response in chronic hepatitis C patients undergoing PEGylated interferon/ribavirin therapy: A meta-analysis. Hum Immunol. 2016;77(7):609-15.
7. O'Brien TR, Pfeiffer RM, Paquin A, Lang Kuhs KA, Chen S, Bonkovsky HL, et al. Comparison of functional variants in IFNL4 and IFNL3 for association with HCV clearance. J Hepatol. 2015;63(5):1103-10.
8. Zheng K, Zhang AM. [Correlations between genetic polymorphism of IFN-lambda family gene and HBV infection, virus replication and clearance]. Sheng Wu Gong Cheng Xue Bao. 2022;38(3):893-902.
9. Limothai U, Wasitthankasem R, Poovorawan Y, Tangkijvanich P. Single Nucleotide Polymorphism of Interferon Lambda-4 Gene is not Associated with Treatment Response to Pegylated Interferon in Thai Patients with Chronic Hepatitis B. Asian Pac J Cancer Prev. 2015;16(13):5515-9.
10. Fan JH, Hou SH, Qing-Ling L, Hu J, Peng H, Guo JJ. Association of HLA-DQ and IFNL4 polymorphisms with susceptibility to hepatitis B virus infection and clearance. Ann Hepatol. 2016;15(4):532-9.
11. Fensterl V, Chattopadhyay S, Sen GC. No Love Lost Between Viruses and Interferons. Annu Rev Virol. 2015;2(1):549-72.
12. Hermant P, Demarez C, Mahlakoiv T, Staeheli P, Meuleman P, Michiels T. Human but not mouse hepatocytes respond to interferon-lambda in vivo. PLoS One. 2014;9(1):e87906.
13. Misumi I, Whitmire JK. IFN-lambda exerts opposing effects on T cell responses depending on the chronicity of the virus infection. J Immunol. 2014;192(8):3596-606.
14. Li Y, Cheng H, Zuo X-b, Sheng Y-j, Zhou F-s, Tang X-f, et al. Association analyses identifying two common susceptibility loci shared by psoriasis and systemic lupus erythematosus in the Chinese Han population. Journal of medical genetics. 2013;50(12):812-8.
15. Langhans B, Kupfer B, Braunschweiger I, Arndt S, Schulte W, Nischalke HD, et al. Interferon-lambda serum levels in hepatitis C. J Hepatol. 2011;54(5):859-65.
16. De Re V, Tornesello ML, De Zorzi M, Caggiari L, Pezzuto F, Leone P, et al. PDCD1 and IFNL4 genetic variants and risk of developing hepatitis C virus-related diseases. Liver Int. 2021;41(1):133-49.
17. Sorrentino L, Silvestri V, Oliveto G, Scordio M, Frasca F, Fracella M, et al. Distribution of Interferon Lambda 4 Single Nucleotide Polymorphism rs11322783 Genotypes in Patients with COVID-19. Microorganisms. 2022;10(2).
18. Onabajo OO, Muchmore B, Prokunina-Olsson L. The IFN-lambda4 Conundrum: When a Good Interferon Goes Bad. J Interferon Cytokine Res. 2019;39(10):636-41.
19. Wu H, Zhao G, Qian F, Liu K, Xie J, Zhou H,et al. Association of IL28B polymorphisms with peginterferon treatment response in Chinese Han patients with HBeAg-positive chronic hepatitis B. Liver Int. 2015;35(2):473-81.
20. Seto WK, Wong DK, Kopaniszen M, Proitsi P, Sham PC, Hung IF,et al. HLA-DP and IL28B polymorphisms: influence of host genome on hepatitis B surface antigen seroclearance in chronic hepatitis B. Clin Infect Dis. 2013 ;56(12):1695-703.
21. Chihab H, Badre W, Tahiri M, Jadid FZ, Zaidane I, Elfihry R,et al. IFNL4 rs12979860 polymorphism influences HBV DNA viral loads but not the outcome of HBV infection in Moroccan patients. Microbes Infect. 2021 ;23(4-5):104802.
22. Lee DH, Cho Y, Seo JY, Kwon JH, Cho EJ, Jang ES,et al.Polymorphisms near interleukin 28B gene are not associated with hepatitis B virus clearance, hepatitis B e antigen clearance and hepatocellular carcinoma occurrence. Intervirology. 2013;56(2):84-90.
23. Martin MP, Qi Y, Goedert JJ, Hussain SK, Kirk GD, Hoots WK,et al.IL28B polymorphism does not determine outcomes of hepatitis B virus or HIV infection. J Infect Dis. 2010 ;202(11):1749-53.

Osmangazi Journal of Med, 2025;47(1): 8-15
DOI: 10.20515/otd. 1529100

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Can New Advanced Clinical Parameters Be Used in the Diagnosis of Vitamin B12 Deficiency?

B12 Vitamini Eksikliğinin Tanısında Yeni Gelişmiş Klinik Parametreler Kullanılabilir mi?

[1]Yavuz Uzun, [2]Evin Kocaturk, [2]Zeynep Kusku Kıraz, [3]Hava Uskudar Teke

[1]Eskisehir Osmangazi University Health Sciences Institute, Department of Medical Biochemistry, Eskisehir, Türkiye
[2]Eskisehir Osmangazi University Faculty of Medicine, Department of Medical Biochemistry, Eskisehir, Türkiye
[3]Eskisehir Osmangazi University Faculty of Medicine, Department of Hematology, Eskisehir, Türkiye

ORCID ID of the authors
YU. 0000-0003-1016-5151
EK. 0000-0001-7434-4234
ZKK. 0000-0001-7375-8486
HÜT. 0000-0002-4434-4580

Correspondence / Sorumlu yazar:
Evin KOCATÜRK –

Eskisehir Osmangazi University Faculty of Medicine, Department of Medical Biochemistry, Eskisehir, Türkiye

e-mail: drekocaturk@gmail.com

Abstract: The measurement of vitamin B12 levels has low sensitivity for the diagnosis of vitamin B12 deficiency, therefore, clinicians may prefer to decide the deficiency with the patient's clinic. In this study, the diagnostic values of the classical and advanced clinical complete blood count parameters were investigated to find a new marker in the diagnosis of vitamin B12 deficiency. 150 adult volunteers were included in the study and volunteers were divided into two groups according to their vitamin B12 levels (with or without vitamin B12 deficiency) and hemoglobin levels (with or without anemia). The differences and correlations of laboratory test results between groups were examined. Equivalent of reticulocyte hemoglobin, equivalent of erythrocyte hemoglobin and delta-hemoglobin were found significant differences between groups with or without vitamin B12 deficiency. Hypo-hemoglobinised red cells and hyper-hemoglobinised red cells were found significant difference between groups with or without anemia. Significant positive correlations were found between vitamin B12 levels and equivalent of reticulocyte hemoglobin, equivalent of erythrocyte hemoglobin and delta-hemoglobin. Significant positive correlations were found between hemoglobin levels and macrocytic red blood cells, equivalent of reticulocyte hemoglobin, equivalent of erythrocyte hemoglobin, delta hemoglobin and hyper-hemoglobinised red cells; negative correlations with microcytic red blood cells and hypo-hemoglobinised red cells. It is suggested that these advanced clinical parameters of complete blood count analysis may be used to determine vitamin B12 deficiency.
Keywords: Vitamin B12 deficiency, Anemia, Complete Blood Count, Erythrocytes, Reticulocytes

Özet: B12 vitamini düzeylerinin ölçümünün B12 vitamini eksikliği tanısında duyarlılığı düşüktür, bu nedenle, klinisyenler eksikliğe hastanın kliniği ile karar vermeyi tercih edebilir. Bu çalışmada B12 vitamini eksikliği tanısında yeni bir belirteç bulmak amacıyla klasik ve ileri klinik tam kan sayımı parametrelerinin tanısal değerleri araştırıldı. Çalışmaya 150 yetişkin gönüllü dahil edildi ve gönüllüler B12 vitamini düzeylerine (B12 vitamini eksikliği olan veya olmayan) ve hemoglobin düzeylerine (kansızlık olan veya olmayan) göre iki gruba ayrıldı. Laboratuvar test sonuçlarının gruplar arasındaki farklılıkları ve korelasyonları incelendi. B12 vitamini eksikliği olan ve olmayan gruplar arasında retikülosit hemoglobini, eritrosit hemoglobin ve delta-hemoglobin açısından anlamlı farklar bulundu. Anemisi olan ve olmayan gruplar arasında hipo-hemoglobinize eritrositler ve hiper-hemoglobinize kırmızı hücreler arasında anlamlı fark bulundu. B12 vitamini düzeyleri ile retikülosit hemoglobini, eritrosit hemoglobin ve delta-hemoglobin arasında anlamlı pozitif korelasyon bulundu. Hemoglobin seviyeleri ile makrositik eritrositler, retikülosit hemoglobini, eritrosit hemoglobini, delta hemoglobin ve hiper-hemoglobinize eritrositler arasında anlamlı pozitif korelasyonlar; mikrositik eritrositler ve hipo-hemoglobinize eritrosit düzeyleri ile negatif korelasyonlar bulundu. Tam kan sayımı analizinin bu ileri klinik parametrelerinin B12 vitamini eksikliğini belirlemek için kullanılabileceği öne sürülmektedir.
Anahtar Kelimeler: B 12 Vitamini Eksikliği, Anemi, Tam kan sayımı, Eritrositler, Retikülositler

Ethics Committee Approval: This study was designed and conducted in accordance with the ethical guidelines set forth in the Declaration of Helsinki, and the study protocol was approved by the Eskisehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (Date: 16.10.2020, Decision No:23).

Informed Consent: This study did not require informed consent.

Authorship Contributions: Concept: YU, EK, ZKK Design: YU, EK, ZKK, HUT Data Collection or Processing: YU, EK, HUT. Analysis or Interpretation: YU, EK. Literature Search: YU, EK. Writing: YU, EK, ZKK, HUT.

Copyright Transfer Form: Copyright Transfer Formwas signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Received 07.08.2024

Accepted : 06.11.2024

Published : 12.11.2024

How to cite/ Atıf için: Uzun Y, Kocaturk E, Kusku Kıraz Z, Uskudar Teke H, Can New Advanced Clinical Parameters Be Used in the Diagnosis of Vitamin B12 Deficiency?, Osmangazi Journal of Medicine, 2025;47(1): 8-15.

1. Introduction

Megaloblastic anemia that is in the macrocytic anemia group morphologically and often occurs due to vitamin B12 deficiency is an important hematological disorder (1). The first test to evaluate the vitamin B12 metabolism is serum vitamin B12 measurement, but metabolically active form of vitamin B12 cannot be measured by this assay, so the sensitivity is low (2, 3). Measurements of plasma homocysteine, serum/urine methyl malonic acid (MMA), and serum holo transcobalamin are used to evaluation of vitamin B12 metabolism (4). Since plasma homocysteine level also changes in the deficiency of vitamin B6 and folic acid, its diagnostic specificity is limited (5). Although serum/urine MMA measurement is more specific than the plasma homocysteine measurement, its use is limited due to the high cost and difficulty of the measurement procedure (6). Although the active form of vitamin B12, holo transcobalamin, may be measured, it is not yet a widely used as a diagnostic test since it may be affected by the transcobalamin 2 carrier protein synthesis defect, too. Therefore, new diagnostic tests are needed for the diagnosis of vitamin B12 deficiency (7, 8).

In the detection of vitamin B12 deficiency, the significance of complete blood count parameters is being investigated, but the sensitivity and specificity of classical parameters are not enough (9), therefore, the use of reticulocyte (RET) counts and indexes has been tried (10).

Sysmex XN series complete blood count analyzers measure or calculate advanced clinical parameters as percentage of microcytic and macrocytic red blood cells (MicroR and MacroR), hypo-hemoglobinised red cells (HYPO-He, percentage of RBCs with a hemoglobin content of less than 17 pg.) and hyper-hemoglobinised red cells (HYPER-He, percentage of RBCs with a hemoglobin content of more than 49 pg.), equivalent of reticulocyte hemoglobin (RET-He) and delta hemoglobin (Delta-He, subtraction between amount of mature RBC hemoglobin and RET-He) (11, 12). Measurements of these advanced clinical parameters are performed in the reticulocyte channel.

In this study, the diagnostic values of the classical and advanced clinical blood count parameters were investigated in vitamin B12 deficiency and it was aimed to find a new diagnostic marker that is more compatible with the clinic.

2. Materials and Methods

This study was conducted with the approval of the local ethics committee and 150 adult volunteers whose vitamin B12 and folic acid measurements and complete blood count analyses were performed in our hospital's biochemistry laboratory, were included in the study.

Patients with other diseases that cause macrocytic anemia, such as leukemia multiple myeloma, whose mean corpuscular volume (MCV) below 90 fL, folic acid level below 4.6 ng/mL, serum creatinine level above 1.2 mg/dL in women and 1.3 mg/dL in men and who take vitamin B12 supplements (if their vitamin B12 level higher than 400 pg/mL) and pregnant women were excluded.

Volunteers were divided into two groups firstly according to their vitamin B12 levels (with or without vitamin B12 deficiency) and then hemoglobin (Hb) levels (with or without anemia).The cut-off values of vitamin B12 for the diagnosis of deficiency was accepted as 197 pg/mL that is recommended by the manufacturer and used in our routine laboratory (Insert.Elecsys Vitamin B12 II.07028121500.V7.tr) and the cut-off values of Hb for the diagnosis of anemia were accepted as 13.5 g/dL in men and 11.9 g/dL in women that are used in our routine laboratory for adults and in accordance with the literature (13). The differences and correlations of laboratory test results between groups were examined.

Serum creatinine, vitamin B12 and folic acid levels were measured by Cobas 8000 auto analyzer (Roche Diagnostics, Mannheim, Germany). The Jaffe method was used for creatinine measurement, and the electro chemiluminescence immunoassay for vitamin B12 and folic acid measurements. Complete blood count and reticulocyte count were examined by Sysmex XN 9000 automatic blood count analyzer (Sysmex Corporation, Kobe, Japan).

Statistical analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to decide the distribution of variables. Data with normal distribution were given as mean ± standard deviation, and data not with normal distribution were given as median (25th-75th quartile). Independent samples t test or Mann-Whitney U was applied as appropriate. Pearson or Spearman correlation tests were applied for showing the associations between variables. Receiver

Operating Characteristic (ROC) Curve analysis was conducted to determine the effects of the markers via areas under the ROC curve (AUC). All data analyses were performed with SPSS package program and P<0.05 level was considered statistically significant.

3. Results

150 volunteers were included in the study with the mean age of 54 years. Laboratory results of groups that were divided according to vitamin B12 levels are shown in Table 1. Hematocrit (HCT), red blood cell (RBC), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell (WBC), RET-He, RBC-He and Delta-He levels were significant difference between groups (Table 1). Laboratory results of groups that were divided according to Hb levels are shown in Table 2. Vitamin B12, HCT, RBC, MCV, RET%, Hypo-He and Hyper-He levels were significant difference between groups (Table 2).

Significant positive correlations were found between vitamin B12 levels and MCH, MCHC, absolute reticulocyte count (RET#), RET%, RET-He, RBC-He and Delta-He; negative correlations with HCT and RBC levels. Significant positive correlations were found between Hb levels and HCT, RBC, MCH, MCHC, MacroR, WBC, RET-He, RBC-He, Delta-He and HYPER-He; negative correlations with Micro-R, RET% and HYPO-He (Table 3).

ROC analysis was conducted to determine the effects of the new significant markers for each group and AUCs are shown in Table 4. All parameters were also significant and the AUCs were above 0.65 (Figure 1 and 2).

Table 1. Laboratory results of groups that were divided according to vitamin B12 levels

	Group 1 (n=46)	**Group 2** (n=104)	***P***
Age (years)	53 (40-60)	54 (44-61)	0.281
Vitamin B12 (pg/mL)	173 (153-183)	359 (248-505)	<0.001
Folic acid (ng/mL)	7.72 (6.40-10.2)	8.35 (6.16-10.8)	0.454
Hb (g/dL)	14.6 ± 1.59	14.1 ± 1.65	0.114
HCT (%)	43.2 ± 4.20	41.0 ± 4.43	**0.008**
RBC (10^6/µL)	4.69 ± 0.48	4.42 ± 0.51	**0.004**
MCV (fL)	91.3 (90.6-93.1)	92.0 (90.7-94.2)	0.140
MCH (pg)	32.0 ± 1.23	31.8 ± 1.43	**0.001**
MCHC (%)	33.7 ± 1.12	34.3 ± 1.03	**0.002**
Micro-R (%)	0.90 (0.70-1.10)	0.90 (0.70-1.10)	0.669
Macro-R (%)	3.75 (3.58-4.03)	3.70 (3.40-4.10)	0.477
Platelets (10^3/µL)	249 ± 70	239 ± 74	0.293
White blood cells (10^3/µL)	7.52 ± 2.02	6.72 ± 1.98	**0.029**
RET# (10^3/µL)	0.07 (0.06-0.08)	0.07 (0.05-0.09)	0.257
RET%	1.45 (1.22-1.70)	1.51 (1.24-1.98)	0.071
RET-He (pg)	32.7 ± 1.41	33.8 ± 1.64	**<0.001**
RBC-He (pg)	30.2 ± 1.15	30.8 ± 1.15	**0.005**
DELTA-He (pg)	2.50 (1.98-3.00)	2.85 (2.40-3.38)	**0.008**

HYPO-He (%)	0.10 (0.10-0.20)	0.10 (0.10-0.20)	0.326
HYPER-He (%)	0.70 (0.60-0.80)	0.70 (0.60-0.80)	0.120

Independent samples t test (mean ± standard) and Mann-Whitney U test (median, 25th and 75th quartile) were applied.

Table 2. Laboratory results of groups that were divided according to hemoglobin levels

	Group A (n=20)	**Group B** (n=130)	***P***
Age (years)	60 (50-62)	53 (42-59)	0.047
Vitamin B12 (pg/mL)	430 (269-528)	232 (182-408)	**0.004**
Folic acid (ng/mL)	8.60 (5.97-10.2)	7.80 (6.46-10.6)	0.668
Hb (g/dL)	11.9 ± 1.09	14.6 ± 1.41	**<0.001**
HCT (%)	35.2 ± 3.37	42.7 ± 3.71	**<0.001**
RBC (10^6/µL)	3.73 ± 0.41	4.62 ± 0.42	**<0.001**
MCV (fL)	93.6 (91.8-95.9)	91.4 (90.7-93.6)	**0.004**
MCH (pg)	32.03 ± 2.01	31.5 ± 1.30	0.146
MCHC (%)	33.9 ± 1.41	34.1 ± 1.04	0.594
Micro-R	0.90 (0.73-1.40)	0.90 (0.70-1.10)	0.166
Macro-R	3.70 (3.13-5.63)	3.70 (3.50-4.00)	0.833
Platelets (10^3/µL)	232 (187-290)	228 (193-283)	0.738
White blood cells (10^3/µL)	6.41 (4.37-8.87)	6.66 (5.70-8.12)	0.621
RET# (10^3/µL)	0.06 (0.05-0.09)	0.07 (0.06-0.08)	0.772
RET%	1.77 (1.30-2.38)	1.48 (1.21-1.75)	**0.034**
RET-He (pg)	33.6 ± 2.34	33.4 ± 1.53	0.735
RBC-He (pg)	30.7 (30.1-31.2)	30.7 (29.9-31.3)	0.954
DELTA-He (pg)	2.70 (1.93-4.20)	2.70 (2.30-3.23)	0.951
HYPO-He (%)	0.25 (0.10-0.58)	0.10 (0.10-0.20)	**0.001**
HYPER-He (%)	0.60 (0.53-0.70)	0.70 (0.60-0.80)	**0.039**

Independent samples -t test (mean ± standard) and Mann-Whitney U test (median, 25th and 75th quartile) were applied. Group A is with anemia, Group B without anemia

Table 3. Correlations of laboratory tests between vitamin B12 and Hb levels

	Vitamin B12		**Hb**	
	r	***P***	**r**	***P***
Hb	-0.156	0.056	1	
HCT	-0.222	**0.006**	0.951	**<0.001**
RBC	-0.232	**0.004**	0.913	**<0.001**
MCV	0.134	0.103	-0.128	0.117
MCH	0.188	**0.021**	0.254	**0.002**
MCHC	0.173	**0.034**	0.380	**<0.001**
MicroR	0.043	0.598	-0.264	**0.001**
MacroR	0.015	0.857	0.334	**<0.001**
Platelet	-0.018	0.831	-0.116	0.158
White blood cell	-0.097	0.238	0.169	**0.039**
RET#	0.224	**0.006**	0.150	0.068
RET%	0.272	**0.001**	-0.170	**0.038**
RET-He	0.251	**0.002**	0.317	**<0.001**
RBC- He	0.197	**0.016**	0.308	**<0.001**
DELTA- He	0.220	**0.007**	0.161	**0.048**
HYPO- He	0.139	0.091	-0.505	**<0.001**
HYPER- He	0.139	0.091	0.636	**<0.001**

Pearson or Spearman correlation test was applied as appropriate.

Table 4. Results of ROC analyses

	AUC	**P**
For the groups that were divided according to vitamin B12 levels		
RET-He	0.680	< 0.001
RBC-He	0.641	0.006
DELTA-He	0.635	0.008
For the groups that were divided according to hemoglobin levels		
RET%	0.647	0.034
HYPO-He	0.702	0.004
HYPER-He	0.639	0.046

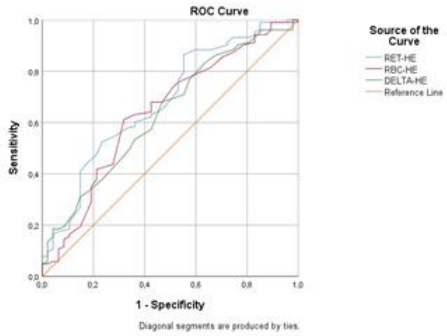


Figure 1. ROC curves groups that were divided according to vitamin B12 levels

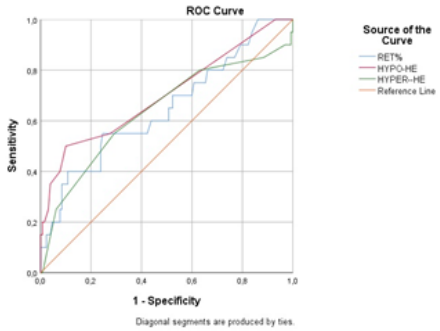


Figure 2. ROC curves the groups that were divided according to hemoglobin levels

4. Discussion

Vitamin B12 deficiency is common and causes megaloblastic anemia (14), and the first and most common laboratory test is the measurement of serum vitamin B12 level to determine vitamin B12 deficiency (2, 15). The cut-off value for vitamin B12 deficiency is accepted as 200 pg/mL. Vitamin B12 levels below this value indicate the risk of anemia (15). In this study, the cut-off value of vitamin B12 deficiency was accepted as 197 pg/mL that is used in our routine laboratory.

According to results of this study, vitamin B12 deficiency rate was 35%. The first remarkable finding was that there was no difference in Hb levels between the groups with and without vitamin B12 deficiency (Table 1). At the beginning of the study, the patients who had other causes of macrocytic anemia, with mean corpuscular volume (MCV) below 90 fL and folic acid level below 4.6 ng/mL were excluded, therefore we expected to find low Hb levels in the group with vitamin B12 deficiency, but this expect did not happen. Likewise, contrary to our expectations, RBC and HCT levels were significantly higher, MCH and MCHC levels were significantly lower in vitamin B12 deficiency group (P=0.004, P=0.008, P= 0.001, P=0.002, respectively) (Table 1). Pancytopenia, which is expected to be seen in vitamin B12 deficiency (16), was not observed in our study. All forms of vitamin B12 are measured by serum vitamin B12 assay, that's why this assay's diagnostic specificity is not high (3), therefore, the serum vitamin B12 levels may not always show parallelism with the clinicopathological findings of the vitamin B12 deficiency (17). This situation was also supported by these results of the study.

When it was determined that the clinic of vitamin B12 deficiency and serum vitamin B12 levels did not show parallelism, the participants were grouped according to their Hb levels and the groups with and without anemia were compared. As expected, HCT and RBC levels were significantly lower and MCV levels were significantly higher in the anemia group (Table 2). Contrary to expectations, vitamin B12 level was significantly higher in the anemia group

(Table 2). At the same time, it was found that vitamin B12 level had negative correlations with Hb, HCT and RBC levels, and positive correlations with MCV, MCH and MCHC (Table 3). These results also showed us that the level of vitamin B12 does not correlate accurately with clinicopathological findings of vitamin B12 deficiency.

As far as we know, this is the first study that examine advanced clinical parameters of Sysmex in vitamin B12 deficiency. According to the results of the study, it was found that RET-He, RBC-He and Delta-He levels were significantly lower in the group with Vitamin B12 deficiency (P=<0.001, P=0.005 and P=0.008, respectively). In addition, positive significant correlations were found between these three parameters and vitamin B12 levels. It was thought that these parameters, which were shown to be significant in iron deficiency anemia (18, 19) and used to differentiate between various disease-specific types of anemia (20), could also be used as new markers in vitamin B12 deficiency. On the other hand, it was found that Hypo-He level had significantly higher and Hyper-He level was significantly lower in the anemia group, and Hb level had negative correlation with Hypo-He and positive correlation with Hyper-He. These findings revealed that these parameters may be new markers for the diagnosis of vitamin B12 deficiency. All these new parameters were analysed by ROC curve and this analysis showed that these parameters can be used in the diagnosis of vitamin B12 deficiency.

Although there was no difference between the study groups, it was found that Hb level had negative correlation with MicroR, and positive correlation with MacroR. These correlations may be a focus point for other studies.

In our study, patients with other diseases that cause macrocytic anemia were excluded and patients with high MCV levels were included in the study, therefore, it was thought that the cause of anemia was vitamin B12 deficiency. This situation and the numerical difference between the groups may be a limitation of the study however it is not always possible to make a definitive diagnosis of vitamin B12.

In conclusion, the results of this study support that serum vitamin B12 levels do not accurately indicate the clinic of vitamin B12 deficiency, therefore it is suggested that the new studies may be conducted to use of easily measurable advanced clinical parameters such as RET-He, RBC-He, Delta-He, Hypo-He and Hyper-He in the diagnosis and follow-up of patients with vitamin B12 deficiency

REFERENCES

1. Carmel R. Current concepts in cobalamin deficiency. Annu Rev Med. 2020;51:357-375.
2. Hvas AM, Nexo E. Diagnosis and treatment of vitamin B 12 deficiency. An update. Haematologica. 2006;91:1506-1512.
3. Kesiktaş N, Eskiyurt N, Karan A, et al. Relation of Vitamin B12 Levels to Bone Mineral Density of Postmenopausal Women. Turk J Osteoporos. 2009;15:1-6.
4. Hannibal L, Lysne V, Bjørke-Monsen AL, et al. Biomarkers and Algorithms for the Diagnosis of Vitamin B12 Deficiency. Front Mol Biosci. 2016;27:3:27.
5. Refsum H, Smith AD, Ueland PM, et al. Facts and recommendations about total homocysteine determinations: an expert opinion. Clin Chem. 2004;50:3–32.
6. Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency. Arch Intern Med. 1999;159:1289-1298.
7. Barbosa PR, Stabler SP, Machado AL, et al Association between decreased vitamin levels and MTHFR, MTR and MTRR gene polymorphisms as determinants for elevated total homocysteine concentrations in pregnant women. Eur J Clin Nutr. 2008;62:1010–1021.
8. Metz J, Bell AH, Flicker L, et al. The significance of subnormal serum vitamin B12, concentration in older people: a case control study. J Am Geriatr Soc. 1996;44:1355–1361.
9. Thomson ABR, Sauve MD, Kassam N, Kamitakahara H. Safety of the long-term use of proton pump inhibitors. World J Gastroenterol. 2010;16(19):2323–2330.
10. Emen B, Öztürk Y, Eren MA, et al. Retrospective Analysis of the Correlation of Etiological Factors with Laboratory Features in Vitamin B12 Defficient Patients. The journal of Tepecik Education and Research Hospital. 2013;23(1):19-23.
11. Advanced clinical and research parameters in haematology. (sysmex-europe website). https://www.sysmex-europe.com/academy/knowledge-centre/sysmex-parameters.html Accessed October 14, 2021.
12. Schapkaitz E. Stability of New Erythrocyte and Reticulocyte Parameters in Testing for Anemia on the Sysmex XN 9000. Lab Med. 2018;49(3):219-225.

13. Badireddy M, Baradhi KM. Chronic Anemia. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Bookshelf ID: NBK534803, https://www.ncbi.nlm.nih.gov/books/NBK534803/
14. Nielsen MJ, Rasmussen MR, Andersen CB, et al. Vitamin B12 transport from food to the body's cells--a sophisticated, multistep pathway. Nat Rev Gastroenterol Hepatol. 2012;9(6):345-354.
15. Carmel R, Green R, Rosenblatt DS, Watkins D. Update on cobalamin, folate, and homocysteine. Hematology Am Soc Hematol Educ Program. 2003;62-81.
16. Ocakçı S. Approach to iron and B12 deficiency anemia in primary care. Smyrna Medical Journal. 2012;1:51-53.
17. Baytan B, Özdemir Ö, Erdemir G, Güneş AM. Vitamin B12 Deficiency: The Clinical Features and Treatment During Childhood. Journal of Uludağ University Medical Facult. 2007;33:61-64.
18. Maconi M, Cavalca L, Danise P, et al. Erythrocyte and reticulocyte indices in iron deficiency in chronic kidney disease: comparison of two methods. Scand J Clin Lab Invest. 2009;69(3):365–370.
19. Toki Y, Ikuta K, Kawahara Y, et al. Reticulocyte hemoglobin equivalent as a potential marker for diagnosis of iron deficiency. Int J Hematol. 2017;106(1):116–125.
20. Weimann A, Cremer M, Hernáiz-Driever P, Zimmermann M. Delta-He, Ret-He and a New Diagnostic Plot for Differential Diagnosis and Therapy Monitoring of Patients Suffering from Various Disease-Specific Types of Anemia. Clin Lab. 2016;62(4):667-677.

Osmangazi Journal of Med, 2025;47(1): 16-21
DOI: 10.20515/otd. 1486835

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Pain in Spinal Muscular Atrophy Type 2 and Type 3 Patients

Spinal Musküler Atrofi Tip 2 ve Tip 3 Hastalarında Ağrı

Arife Derda Yücel Şen, Özlem Uğur, Coşkun Yarar, Kürşat Bora Çarman

Eskisehir Osmangazi University Health Sciences Institute, Department of Pediatric Neurology, Eskisehir, Türkiye

ORCID ID of the authors
ADYŞ. 0000-0002-2656-5611
ÖU. 0000-0001-9257-085X
ÇY. 0000-0001-7462-4578
KBC. 0000-0002-4629-1873

Correspondence / Sorumlu yazar:
Arife Derda YÜCEL ŞEN–

Eskişehir Osmangazi University Department of Pediatric Neurology, Eskişehir, Türkiye

e-mail: derdayucel@hotmail.com

Abstract: Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by degeneration of alpha motor neurons. It is a multisystemic disease affecting non-neuronal systems and quality of life. We aimed to investigate the prevalence and characteristics of pain in children with spinal muscular atrophy. In this single-center study, by using visual analog scales, 13 patients diagnosed with SMA type 2 and type 3 accompanied by their parents filled out a questionnaire involving questions about the presence of chronic pain, pain frequency, duration, location, and intensity, causes of pain, and coping methods. All patients reported that they experienced chronic pain. Patients with type 3 experienced pain more frequently than those with type 2—multiple times each month. The terms "minutes," "mild," and "intermittent" were most commonly used to describe the length, intensity, and course of the pain in both groups. The mean pain intensity according to Visual Analogue Scale were 35.5□26.3 mm in type 2 and 25.1□10.2 mm in type 3. The localization of pain was primarily concentrated in the back and lower extremities. The most common causes of pain were stretching exercises during physical therapy and posture disorder. The most common methods of coping with pain were distraction strategy and massage. Pain is a common problem in children with SMA. Management of the pain might increase the life quality of SMA patients. A multidisciplinary approach must be considered in the treatment of these children.
Keywords: Spinal muscular atrophy, pain, child

Özet: Spinal musküler atrofi (SMA), alfa motor nöronların dejenerasyonu ile karakterize otozomal resesif geçişli bir nöromusküler hastalıktır. Nöronal olmayan sistemleri ve yaşam kalitesini etkileyen multisistemik bir hastalıktır. Spinal musküler atrofili çocuklarda ağrının prevalansını ve özelliklerini araştırmayı amaçladık. Bu tek merkezli çalışmada, SMA tip 2 ve tip 3 tanısı alan toplam 13 hastaya ebeveynler eşliğinde görsel analog ölçekler kullanılarak kronik ağrının varlığı, ağrı sıklığı, süresi, yeri, şiddeti, ağrı nedenleri ve baş etme yöntemlerinin sorgulandığı bir anket doldurduldu. Çalışma 13 hasta ile yürütüldü ve tüm hastalar kronik ağrı yaşadıklarını bildirdi. Tip 3 hastaları, tip 2 hastalarına göre her ay birkaç kez olmak üzere daha sık ağrı yaşadılar. "Dakika", "hafif" ve "aralıklı" terimleri her iki grupta da ağrının uzunluğunu, yoğunluğunu ve seyrini tanımlamak için kullanıldı. Vizüel Analog Skala'ya göre ortalama ağrı şiddeti tip 2'de 35.5□26.3 mm, tip 3'te ise 25.1□10.2 mm idi. Ağrının lokalizasyonu çoğunlukla sırt ve alt ekstremitelerde yoğunlaştı. Ağrının en sık nedenleri fizik tedavi sırasında yapılan esneme egzersizleri ve duruş bozukluklarıydı. Ağrıyla başa çıkmanın en yaygın yöntemleri dikkat dağıtma stratejisi ve masajdı. SMA'lı çocuklarda ağrı sık görülen bir sorundur. Ağrının yönetimi SMA hastalarının yaşam kalitesini artırabilir. Bu çocukların tedavisinde multidisipliner bir yaklaşım göz önünde bulundurulmalıdır.
Anahtar Kelimeler: Spinal musküler atrofi, ağrı, çocuk

Ethics Committee Approval: The study was approved by Eskisehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 54, Date: 16.05.2023

Informed Consent: This study did not require informed consent.

Authorship Contributions KBC conceived the idea for the study. ADYS, OU and CY contributed to the design and planning of the research. ADYS directed the individuals to study. CY made the interventions. All authors were involved in data collection. ADYS, OU, CY and KBC analyzed the data. ADYS wrote the first draft of the manuscript. All authors edited and approved the final version of the manuscript.

Copyright Transfer Form: Copyright Transfer Formwas signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Received 20.05.2024
Accepted : 18.11.2024
Published : 18.11.2024

How to cite/ Atıf için: Sen Yucel AD, Ugur O, Yarar C, Carman KB, Pain in Spinal Muscular Atrophy Type 2 and Type 3 Patients, Osmangazi Journal of Medicine, 2025;47(1):16-21.

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by degeneration of alpha motor neurons in the spinal cord, causing progressive proximal muscle weakness. The disease is caused by mutations in the SMN1 gene on chromosome 5, which leads to decreased expression of the Survival Motor Neuron (SMN) protein (1). Spinal muscular atrophy is classified into four subtypes according to age of onset and maximum motor development achieved (Table 1).

Table 1. Types of spinal muscular atrophy

Type	Onset	Symptoms	Maximum milestones
0	Prenatal	Respiratory failure, severe hypotonia	
1	0-6 months	Severe deficits in motor function. Difficulties in respiration and/or swallowing, and fasciculation of the tongue.	No sitting
2	<18 months	Severe deficits in motor function. Delay in motor development, weakness, scoliosis, joint contracture	Sitting, no walking
3	>18 months	Variable degrees of weakness, scoliosis, loss of ambulation	Independent walking
4	Adult	Milder weakness	Independent walking

The natural history of SMA has changed radically with the advent of improved standards of care and the availability of disease-modifying therapies. As a result of the emergence of new treatments, a significant increase in patients' quality of life was observed, as there was a dramatic change in the survival rate, the maximum motor function achieved, and the overall progression of the disease. Rehabilitation is necessary for SMA patients to maintain and improve their motor functions and activities of daily living.

Although the nervous system is the main target of SMA, it is a multisystemic disease that affects the quality of life (QOL) of cases. Pain is one factor contributing to patients' QOL (2). Pain is defined as "an unpleasant sensory and emotional experience linked to or characterized by actual or potential tissue damage." The causes of pain in SMA are multifactorial, including excessive muscle use, vertebral fractures and/or orthopedic problems, and respiratory reasons. The expression of pain complaints may also be affected by various psychological factors. Perceived pain associated with SMA or therapeutic procedures may be dismissed or viewed as fate by both patient and caregiver. Therefore, there are difficulties in its recognition and evaluation.

Information about pain in children with SMA is limited. This topic is essential for understanding treatment options, the effect of pain on patient compliance, and the outcomes of other rehabilitation interventions. We aimed to investigate pain characteristics in SMA patients.

2. Materials and Methods

2.1. Study Design and Participants

This cross-sectional survey research was conducted from July 2023 to November 2023. Patients with a confirmed diagnosis of SMA, younger than 18 years of age, who agreed to participate in the survey, and who had no cognitive problems were included in the study. Participants consisted of SMA type II and III patients and their parents.9 SMA type 2 and 4 SMA type 3 patients participated in the study. The questionnaire used in this study was applied during routine outpatient clinic controls. Since the patients were under the age of 18, they answered the questionnaire with the help of their parents. SMA type I patients were excluded from the study due to the different severity of the disease. Patients and their caregivers both signed the informed consent.

2.2. Questionnaire Items and Questions on Pain

The questionnaire items were designed to collect demographic and clinical characteristics and pain status data. The patients were asked whether they had experienced any pain other than occasional headache, abdominal pain, and toothache in the last three months. The questionnaire included questions about the location of pain, frequency of pain, duration of pain, severity of pain, pain affecting activities of daily living, and factors that aggravate and alleviate pain. This study defined pain, under the International Association for the research of Pain (IASP), as an unpleasant sensory and emotional experience linked to or characterized by actual or probable tissue damage (3). Chronic pain was

defined as persistent or recurrent pain lasting longer than three months. Pain caused by headache, dental pain, abdominal pain, or psychological pain was excluded from the analysis. The location of pain was assessed using a body map where the location of pain could be marked. The severity of pain was evaluated using the Visual Analogue Scale (VAS).

VAS has been used since the 1920s to evaluate abstract quantities such as pain, quality of life, and anxiety. In VAS, pain sections consist of a line, usually 100 mm long, with descriptions such as "no pain" and "worst pain imaginable." The patient places a mark reflecting his pain, and the distance from the left endpoint to the mark is measured in mm. VAS was first used in psychology to measure mood disorders and, since the mid-1960s, to measure pain. The scale can be horizontal or vertical. VAS is used in daily clinical practice both as a research tool and for repeated measurements to manage chronic pain (4).

2.3. Statistical analysis

The Statistical Package for the Social Sciences (SPSS) for Windows 21 was used for the statistical analysis. Descriptive statistics provided numerical data and percentages regarding demographic and clinical characteristics, prevalence, frequency, duration, and location. The frequency of factors that aggravate or alleviate pain was also evaluated. Age was represented using mean values and standard deviations. The severity of pain and the discomfort it induces were assessed, and the median and range of the VAS and numerical rating scales were determined to evaluate pain interference.

2.4. Ethics Notification

The study was conducted in compliance with the principles of the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. The study was approved by the Local Ethical Committee.

3. Results

The study was conducted with thirteen SMA patients. The mean age of cases was calculated as 128.4±50.5 months of age. The majority of patients were non-ambulatory. Tracheostomy and gastrostomy were present in two cases. One type 2 SMA case had scoliosis surgery previously. Demographic data and motor functions of the patients were shown in Table 2.

Table 2. Demographic and clinical characteristics study group.

	SMA Type 2	SMA Type 3	Total
Sex			
Female	7	2	9
Male	2	2	4
Mean age (months)	118.7± 49.9	150.2± 51.7	128.4± 50.5
Ambulation status			
Non-ambulatory	8	0	8
Ambulatory	1	4	5

All patients reported that they had experienced pain. Among SMA patients, the course of pain was mostly intermittent in both groups. The two patients who described constant pain were non-ambulatory patients with SMA type 2 and tracheostomy and gastrostomy. Pain experienced several times a month was more frequent in patients with type 3 than in patients with type 2. Duration of pain was most frequently reported as 'minutes' in both groups. The mean pain intensity according to VAS was 35.5±26.3 mm in type 2 patients and 25.1±10.2 mm in type 3 patients. In both groups, the severity of pain was most frequently rated as 'mild' by the patients. The localization of pain was primarily concentrated in the back and lower extremities. The most common causes of pain were stretching exercises during physical therapy and posture disorder. The most common methods of coping with pain were distraction strategy and massage. The features of pain status were presented in Table 3.

Table 3. The features of pain in the study group.

	SMA Type 2	SMA Type 3	Total
Pain in the last 3 months	9	4	13
Course of pain			
Intermittent	7	4	11
Continuous	2	0	2
Pain frequency			
Several times a day	3	0	3
Several times a week	3	1	4
Several times a month	3	3	6
Duration of pain			
Seconds	1	0	1
Minutes	6	4	10
An hour	1	0	1
Several hours	1	0	1
VAS* (mm)	35.5±26.3	25.1±10.2	32.3±22.4
Severity of pain			
Mild	5	3	8
Moderate	2	1	3
Severe	2	0	2
Localization of pain			
Neck	0	0	0
Arms	0	0	0
Legs	2	3	5
Back	4	0	4
Feet	3	1	4
When the pain occurs			
Overstrain	0	1	1
Stretching during physical therapy	3	2	5
Intensive exercise			
Posture disorder	1	1	2
Prosthesis use	4	0	4
	1	0	1
Methods to cope with pain			
Analgesic use	1	0	1
Distraction strategy	4	2	6
Continuation of daily activities	0	1	1
Massage	4	1	5

*SMA: Spinal muscular atrophy, *VAS: Visual Analogue Scale (0-100 mm)*

4. Discussion

Evaluating children with SMA in terms of pain is essential in terms of adequately recognizing pain and providing treatment options for the causes of pain. Valid and reliable pain assessment parameters are available for children. In this study, we described the results of a questionnaire study on pain administered to SMA type 2 and type 3 patients and their families treated at the child neurology clinic of a tertiary university hospital. Chronic pain lasting at least 3 months was described in all patients with SMA type 2 and type 3. Similarly, there are reports in the literature indicating that children with neuromuscular diseases may have chronic pain (5). Uchio et al. conducted a pain questionnaire study in 2018 that included a total of 86 patients with SMA type 2 and type 3. They reported that 40.6% of patients with type 2 and 40.9% of patients with type 3 had chronic pain (6). In a study on the prevalence of pain in neuromuscular diseases, chronic pain was reported in more than two thirds of patients (7). The reason for the higher prevalence of chronic pain in our study may be the fact that the study was conducted in children younger than 18 years of age, the subjective and complex nature of pain, and the administration of the questionnaire with families.

In this study, patients stated that the pain course was primarily intermittent. The patients who described constant pain in the study may describe continuous pain because they were nonambutary, tracheostomized, and gastrostomized. The quality of life of these patients should also be examined (8). In a study investigating the prevalence of pain in children with neuromuscular diseases, the rate of patients with persistent pain was reported as be 4% (9). Inadequate physical activities may affect the

course of pain. Although acute exercises increase pain sensitivity, it was observed that the development of chronic pain was prevented after regular physical activity (10).

In our study, the characteristics of the pain were mainly mild, resolved within minutes, and localized primarily on the lower extremities. Pain concentrated in the lower extremity may worsen due to hypotonicity, increased fatigue, and deterioration of posture (11). In a study conducted with 115 children with a history of neuromuscular disease, the mean VAS was 31.5±24.3 mm(12). In our study, similar to the literature, the mean VAS was 32.3±22.4 mm. Different studies have found that pain rates differ according to the diagnosis of neuromuscular disease (13). Little is known about the details of the nature and impact of chronic pain in patients with neuromuscular disease, but there are studies suggesting that chronic pain is associated with poor quality of life (14).

In our study, stretching exercises and posture disorders during physical therapy were the most common time periods for the pain occurance. This may be due to severe scoliosis and less physical activity in SMA patients (15). The probability of being unable to walk increases with the clinical course of SMA disease and the progression of scoliosis. Pain due to immobility is a common complaint in such patients (16).

The most common methods of coping with pain were distraction strategy and massage. In the literature, studies are show that distraction strategy reduces anxiety (17). Similarly, massage has been reported to be effective in improving pain and function in patients with chronic pain (18).

This study had several limitations. Clinical differences may be observed between SMA types. The small number of cases in this single-center study is also one of its limitations. In the future, the relationship between SMA and chronic pain should be investigated in larger number of patients.

5. Conclusion

SMA is a multisystemic disease affecting quality of life (QOL). Pain is one of the factors contributing to patients' QOL. A multidisciplinary evaluation of pain in children with SMA must be considered.

REFERENCES

1. Cancès C, Richelme C, Barnerias C, Espil C. Clinical features of spinal muscular atrophy (SMA) type 2. Arch Pediatr. 2020;27:7S18-7S22.
2. Bonanno S, Zanin R, Bello L, et al. Quality of life assessment in adult spinal muscular atrophy patients treated with nusinersen. J Neurol. 2022;269:3264-3275.
3. Merskey H, Bogduk N, International Association for the Studyof Pain. Classification of chronic pain:descriptions of chronic pain syndromes and definitions of pain terms. Seattle: IASP Press; 1994.
4. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: Myths, truths and clinical relevance. Scand J Pain. 2016;13:67-75.
5. Engel JM, Kartin D, Carter GT, Jensen MP, Jaffe KM. Pain in youths with neuromuscular disease. Am J Hosp Palliat Care. 2009;26:405-412.
6. Uchio Y, Kajima K, Suzuki H, Nakamura K, Saito M, Ikai T. Pain in Spinal Muscular Atrophy: A Questionnaire Study. Phys Ther Res. 2022;25:150-155.
7. Guy-Coichard C, Nguyen DT, Delorme T, Boureau F. Pain in hereditary neuromuscular disorders and myasthenia gravis: a national survey of frequency, characteristics, and impact. J Pain Symptom Manage. 2008;35:40-50.
8. Padua L, Aprile I, Frusciante R, et al. Quality of life and pain in patients with facioscapulohumeral muscular dystrophy. Muscle Nerve. 2009;40:200-205.
9. Lager C, Kroksmark AK. Pain in adolescents with spinal muscular atrophy and Duchenne and Becker muscular dystrophy. Eur J Paediatr Neurol. 2015;19:537-546.
10. Sluka KA, O'Donnell JM, Danielson J, Rasmussen LA. Regular physical activity prevents development of chronic pain and activation of central neurons. J Appl Physiol (1985). 2013;114:725-733.
11. Schillings ML, Kalkman JS, Janssen HM, van Engelen BG, Bleijenberg G, Zwarts MJ. Experienced and physiological fatigue in neuromuscular disorders. Clin Neurophysiol. 2007;118:292-300.
12. Miró J, de la Vega R, Gertz KJ, Thong ISK, Jensen MP, Engel JM. Do Commonly Used Measures of Pain Intensity Only Reflect Pain Intensity in Youths With Bothersome Pain and a Physical Disability?. Front Pediatr. 2019;7:229.
13. Hoffman AJ, Jensen MP, Abresch RT, Carter GT. Chronic pain in persons with neuromuscular disease. Phys Med Rehabil Clin N Am. 2005;16:1099-xii.
14. Hunt A, Carter B, Abbott J, Parker A, Spinty S, deGoede C. Pain experience, expression and coping in boys and young men with Duchenne Muscular

Dystrophy - A pilot study using mixed methods. Eur J Paediatr Neurol. 2016;20:630-638.
15. Vu-Han TL, Reisener MJ, Putzier M, Pumberger M. Skoliose bei spinaler Muskelatrophie [Scoliosis in spinal muscular atrophy]. Orthopade. 2021;50:657-663.
16. Hanna RB, Nahm N, Bent MA, et al. Hip Pain in Nonambulatory Children with Type-I or II Spinal Muscular Atrophy. JB JS Open Access. 2022;7:e22.00011.
17. Delgado A, Ok SM, Ho D, Lynd T, Cheon K. Evaluation of children's pain expression and behavior using audio visual distraction. Clin Exp Dent Res. 2021;7:795-802.
18. Flynn DM. Chronic Musculoskeletal Pain: Nonpharmacologic, Noninvasive Treatments. Am Fam Physician. 2020;102:465-477.

Osmangazi Journal of Med, 2025;47(1):22-31
DOI: 10.20515/otd. 1550401

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Evaluation of the Proliferative Effects of Hexagonal Boron Nitride Nanoparticles on Leukemia Cells and Leukemia Stem Cells

Altıgen Bor Nitrür Nanopartiküllerinin Lösemi Hücreleri ve Lösemi Kök Hücreleri Üzerindeki Proliferatif Etkilerinin Değerlendirilmesi

[1]Neslihan Meriç, [2]Fatih Kar, [3]Ezgi Kar

[1]Faculty of Engineering and Natural Sciences, Department of Molecular Biology and Genetics, Kütahya Health Sciences University, Kütahya, Türkiye
[2]Faculty of Medicine, Department of Biochemistry, Kütahya Health Sciences University, Kütahya, Türkiye
[3]Faculty of Health Sciences, Department of Nutrition and Dietetics, Kütahya Health Sciences University, Kütahya, Turkiye

ORCID ID of the authors
NM. 0000-0002-2878-5052
FK. 0000-0001-8356-9806
EK. 0000-0003-2134-4067

Correspondence / Sorumlu yazar:
Neslihan MERİÇ
Faculty of Engineering and Natural Sciences, Department of Molecular Biology and Genetics, Kütahya Health Sciences University, Kütahya, Türkiye
e-mail: neslihan.meric@ksbu.edu.tr

Abstract: Leukemia is a malignant disease that affects the bone marrow, lymphatic system, spleen, and blood-forming organs, leading to an excessive proliferation of white blood cells. Current cancer treatments are often limited by drug resistance, highlighting the need for novel therapeutic strategies. Nanoparticles, including boron nitride (BN) nanomaterials, have shown promise in enhancing drug delivery and therapeutic efficacy due to their excellent physical and chemical properties. This study aimed to evaluate the cytotoxic effects of hexagonal boron nitride nanoparticles (hBN NPs) on leukemia cells and leukemia stem cells to explore their potential use in leukemia treatment.: hBN NPs were synthesized and characterized using X-ray powder diffraction (XRD), Scanning Electron Microscopy (SEM), and Transmission Electron Microscopy (TEM). Leukemia cell lines (HL-60 and CCRF-CEM) and CD34+ leukemia stem cells were treated with various hBN NPs. Cell viability was assessed using MTS assays, and flow cytometry was employed to analyze the expression of leukemia surface markers. The study found that hBN NPs did not exhibit significant anticancer properties; instead, they promoted cell proliferation in leukemia cells and stem cells. The CCRF-CEM CD34+ cells showed resistance to hBN NPs treatment, which reduced the treatment's therapeutic efficacy. The lack of cytotoxicity toward healthy cells suggests potential selectivity, yet the proliferative effects on leukemia cells indicate that hBN NPs may not be suitable for leukemia treatment. hBN NPs lack therapeutic potential for leukemia due to their proliferative effects on leukemia cells. Future studies should focus on developing combination therapies and exploring hBN NPs' impact on other cell lines to identify potential synergistic strategies that could overcome resistance mechanisms in leukemia and other cancers.
Keywords: Leukemia, Hexagonal Boron Nitride Nanoparticles, Cytotoxicity

Özet: Lösemi, kemik iliğini, lenf sistemini, dalağı ve kan oluşturan organları etkileyen ve beyaz kan hücrelerinin aşırı çoğalmasına yol açan kötü huylu bir hastalıktır. Mevcut kanser tedavileri genellikle ilaç direnciyle sınırlıdır ve bu da yeni tedavi stratejilerine olan ihtiyacı vurgulamaktadır. Bor nitrür (BN) nanomalzemeleri de dahil olmak üzere nanopartiküller, mükemmel fiziksel ve kimyasal özellikleri nedeniyle ilaç iletimini ve tedavi edici etkinliği artırmada umut vadetmektedir. Bu çalışma, lösemi tedavisinde potansiyel kullanımlarını araştırmak için hekzagonal bor nitrür nanopartiküllerinin (hBN NP'leri) lösemi hücreleri ve lösemi kök hücreleri üzerindeki sitotoksik etkilerini değerlendirmeyi amaçlamaktadır. hBN NP'leri, X-ışını toz kırınımı (XRD), Taramalı Elektron Mikroskobu (SEM) ve Transmisyon Elektron Mikroskobu (TEM) kullanılarak sentezlendi ve karakterize edildi. Lösemi hücre hatları (HL-60 ve CCRF-CEM) ve CD34+ lösemi kök hücreleri çeşitli hBN NP konsantrasyonlarıyla tedavi edildi. Hücre canlılığı MTS analizleri kullanılarak değerlendirildi ve lösemi yüzey belirteçlerinin ekspresyonunu analiz etmek için akış sitometrisi kullanıldı. Çalışma, hBN NP'lerinin önemli antikanser özellikleri göstermediğini; bunun yerine lösemi hücrelerinde ve kök hücrelerinde hücre çoğalmasını teşvik ettiğini buldu. CCRF-CEM CD34+ hücreleri hBN NP tedavisine direnç gösterdi ve bu da tedavinin terapötik etkinliğini azalttı. Sağlıklı hücrelere karşı sitotoksisitenin olmaması potansiyel seçiciliği düşündürmektedir, ancak lösemi hücreleri üzerindeki çoğaltıcı etkiler hBN NP'lerinin lösemi tedavisi için uygun olmayabileceğini göstermektedir. hBN NP'leri lösemi hücreleri üzerindeki çoğaltıcı etkileri nedeniyle lösemi için terapötik potansiyele sahip değildir. Gelecekteki çalışmalar, lösemi ve diğer kanserlerde direnç mekanizmalarının üstesinden gelebilecek potansiyel sinerjistik stratejileri belirlemek için kombinasyon tedavileri geliştirmeye ve hBN NP'lerinin diğer hücre hatları üzerindeki etkisini araştırmaya odaklanmalıdır.
Anahtar Kelimeler: Lösemi, Hekzagonal Bor Nitrür Nanopartikülleri, Sitotoksisite

Ethics Committee Approval: Since this study is an in vitro cell culture study, ethics committee approval is not required. The cell lines used in the study were purchased from the relevant company.

Informed Consent: This study did not require informed consent.

Authorship Contributions: NM formulated the study designs, devised the experiments, and gathered as well as analyzed the data. EK ve FK supported the experimental stages and contributed to analyzing the data.

Copyright Transfer Form: Copyright Transfer Formwas signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Received 15.09.2024
Accepted : 18.11.2024
Published : 19.11.2024

How to cite/ Atıf için: Meriç N, Kar F, Kar E, Evaluation of the Proliferative Effects of Hexagonal Boron Nitride Nanoparticles on Leukemia Cells and Leukemia Stem Cells, Osmangazi Journal of Medicine, 2025;47(1):22-31

1. Introduction

Leukemia is a malignant disease primarily affecting the bone marrow, lymphatic system, spleen, and blood-forming organs. It causes an excessive proliferation of a type of leukocyte, specifically white blood cells (WBCs), leading to leukocytosis (1). Leukemia presents in various forms, some more common in younger patients, while others predominantly affect adults. Although the exact etiology of leukemia remains unknown, several factors, including genetic predisposition, chromosomal abnormalities, chemical agents (such as benzene), chemotherapeutic drugs, radiation, immunodeficiency, and viruses, may contribute to the disease's development (2)

The complex structure of the tumor microenvironment and individual differences between patients make it even more difficult to develop effective cancer treatments. Therefore, research and development of new drug strategies are encouraged.

In recent years, intensive research has been conducted on nanoparticles and this technology has an important place among drug delivery strategies. Nanoparticle-based drug delivery systems have offered significant advantages in cancer treatment and management by providing excellent pharmacokinetic properties, precise targeting, reduced side effects, and superiority against drug resistance. The use of these systems has significant potential in developing more effective cancer interventions (3,4)

The use of nanoparticles (NPs) and nanocarriers in cancer therapy has significantly enhanced the delivery of chemotherapeutic agents, primarily by reducing their toxicity to healthy tissues. NPs offer several advantages, including improved bioavailability, enhanced solubility, extended blood circulation time, and minimized side effects. Furthermore, nano-delivery systems that incorporate targeting or sensing mechanisms have been shown to enhance the efficacy of anti-tumor drug candidates by enabling the selective release of therapeutics at specific target sites (5–7)

Among NPs, boron nitride (BN) nanomaterials have attracted considerable interest due to their excellent physical and chemical properties (8–10). Owing to its high biocompatibility, BN has shown significant potential in drug delivery and cancer treatment applications (11,12). Additionally, BN has been utilized in boron neutron capture therapy (BNCT) for tumor treatment due to its rich 10B content (13–16). However, the surface hydrophobicity of boron nitride nanomaterials facilitates them (17–19)

Cancer stem cells (CSCs) are inherently heterogeneous and exhibit low abundance within tumor populations, which poses challenges for their detection (20,21). Recent advancements in nanotechnology and the development of nanoparticles (NPs) have opened new avenues for the diagnosis and treatment of CSCs, enhancing the precision and effectiveness of therapeutic strategies.

The effects of boron nitride (BN) nanoparticles on leukemia remain largely unknown. To address this gap, our study investigated the cytotoxic effects of newly synthesized hexagonal boron nitride nanoparticles (hBN NP) on leukemia cells and leukemia stem cells, with detailed structural and morphological characterizations performed on the nanoparticles.

2. Materials and Methods

2.1.Synthesis and Characterization of Hexagonal Boron Nitride (hBN) Nanoparticles:

hBN NP was synthesized by reacting boron oxide with ammonia gas, followed by milling in a planetary ball mill and sieving under 150 microns to achieve high crystallinity. In the preparation method, sieving below 150 microns was used, but in the analysis results, the hBN NP size was determined to be 120 nm (22). Characterization was performed using X-ray powder diffraction (XRD) to confirm the crystalline structure, and Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) to analyze the morphology, revealing uniform hexagonal nanoparticles with well-defined features.

The hBN nanoparticles were characterized using imaging and spectroscopic techniques. Before SEM imaging, a conductive Au-Pd layer was sputtered for 40 seconds. SEM analysis revealed a uniform structure with lateral dimensions ranging from 50 to 200 nm and a generally round morphology. TEM imaging confirmed the hexagonal crystalline structure of boron nitride, with particle diameters within 50–200 nm and thicknesses between 15–50 nm. Parallel, straight-line crystalline features characteristic of hBN were observed, further verifying the structural uniformity of the nanoparticles.

Detailed structural and morphological characterization of the hBN nanoparticles used in this study, including SEM, TEM, and XRD analyses, have been previously published (22). The current study focuses on the biological effects of these well-characterized nanoparticles on leukemia cells.

2.2. Propagation of Leukemia Cell Line

HL-60 and CCRF-CEM cell lines obtained from ATCC® (American Type Culture Collection, Manassas, VA, USA) were maintained in RPMI-1640 medium supplemented with 20% fetal bovine serum, 2 mM l-glutamine, 1% PSA (10,000 units/ml penicillin and 10,000 µg/ml streptomycin, and 25 µg/ml of amphotericin B) for their proliferation and the cells were incubated at 37°C in a humidified atmosphere with 5% CO2. Cells were seeded into appropriate culture dishes according to their number and checked daily.

2.3. Obtaining 34+ Stem Cells from Leukemia Cell Lines

When the cells (CCRF-CEM) reached the desired density, they were collected by centrifugation. The cells were washed once with PBS. They were resuspended with PBS again and anti-human CD34+ fluorescently labeled antibodies (Biolegend, USA, Cat. No.343506), were used to selectively bind to CD34+ molecules on the cell surface. After 30 minutes of incubation in the dark, the cells were stained with DAPI. Afterwards, the gate was taken from the live cells and the necessary device adjustments were made and CD34+ cells were separated in the separation device. Before and after the separation in the flow cytometry device, CD34+ and other leukemia cancer markers were analyzed and the effect of the separation process was determined as a percentage (23).

2.4. Identification of CCRF-CEM CD34+ Leukemia Stem Cells Using Monoclonal Antibodies Targeting Leukemia Surface Markers

Following the isolation of CD34+ stem cells from CCRF-CEM cells using a flow cytometry sorting device, the quality of the isolated CCRF-CEM CD34+ cells was assessed by analyzing surface markers both before and after isolation, including CD34+ and other leukemia cancer surface markers (CD34, CD33, CD123, CD133). The impact of the isolation process was quantified as a percentage. The cells were stained with fluorochrome-conjugated antibodies following methodologies consistent with previous studies. For this purpose, leukemia cells were seeded at a density of 50,000 cells/well in a 96-well plate and labeled with leukemia surface antibodies according to the manufacturer's instructions (1:1000 dilution). The labeled cells were then analyzed by flow cytometry (23,24).

2.5. Peripheral Blood Mononuclear Cells (PBMNC)

Peripheral blood mononuclear cells (PBMNCs) isolated from healthy individuals (ATCC®, American Type Culture Collection, Manassas, VA, USA) were utilized as healthy controls. These PBMNCs serve as primary cells that can be directly compared to the leukemia cells under investigation, providing a physiologically relevant baseline for assessing differential cytotoxic effects between normal and cancerous cells. Observing the effects on healthy PBMNCs is critical to confirm that the treatment specifically targets leukemia cells without adversely affecting normal cells.

The isolation of healthy PBMNCs was performed using the classical Ficoll-Paque density gradient centrifugation method. To promote proliferation, PBMNC cultures were sustained in RPMI-1640 medium, enriched with 20% fetal bovine serum, 2 mM L-glutamine, and 1% PSA (comprising penicillin at 10,000 units/ml, streptomycin at 10,000 µg/ml, and amphotericin B at 25 µg/ml). Cultures were incubated at 37°C in a humidified environment with 5% CO_2.

2.6. Cell Cytotoxicity Test

The stock solution of hBN NPs was prepared by dissolving it in physiological serum and then diluted to the desired final concentrations with RPMI. 96 wells were seeded with RPMI medium (50 µL) supplemented with 10% FBS, 1% PSA (10,000 units/ml penicillin and 10,000 µg/ml streptomycin, and 25 µg/ml of Amphotericin B) at 5 x 10^3 cells per well. Then, the cells were treated with diluted concentrations of hBN NPs in four replicates. To determine the appropriate concentrations, initial doses of 10, 20, 40, 80, 160, and 320 µg were prepared, followed by a series of lower diluted concentrations at 2, 4, 6, 8, and 10 µg of hBN NPs. Samples not treated with hBN NPs were used as negative control and samples treated with DMSO 20% were used as positive control. After 24, 48, and 72 hours, MTS solution was added to each well according to the manufacturer's recommendations. MTS solution allows us to determine the number of living cells by causing a color change in the

presence of metabolically active cells that reduce the tetrazolium salt to a formazan dye. This reaction involves the conversion of the tetrazolium salt to formazan by the mitochondrial dehydrogenase activity of the cells. The cells were incubated in the dark at 37°C for 3 hours. The absorbance of the cells was measured at 490 nm. Analysis was performed according to the negative control.

2.7. Statistical Analysis

All data were statistically analyzed using one-way ANOVA or a two-tailed Student's t-test. GraphPad Prism (version 8.0.1) software was utilized for performing the statistical analyses and plotting the graphs. Error bars represent the standard deviation of the mean (SD) from a minimum of three independent experiments. Statistical significance was defined as *P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001, and ****P ≤ 0.0001.

3. Results

3.1. CCRF-CEM CD34+ Leukemia Stem Cells and Leukemia Surface Marker Analysis

Figure 1 illustrates the percentage of CCRF-CEM cells expressing leukemia-associated surface markers (CD34+, CD133+, CD123+, and CD33+) before and after isolation. Before isolation, the expression levels of these markers were generally low, with minimal percentages observed across all groups. Following isolation, there is a marked and statistically significant increase in the percentage of CD34+ cells, identified as Leukemia Stem Cells (LSCs), demonstrating successful enrichment of these cells (****p < 0.0001). Conversely, the percentages of CD133+, CD123+, and CD33+ cells remain relatively unchanged or low post-isolation, suggesting that the isolation process specifically enriches the CD34+ cell population without significantly altering the distribution of other markers.

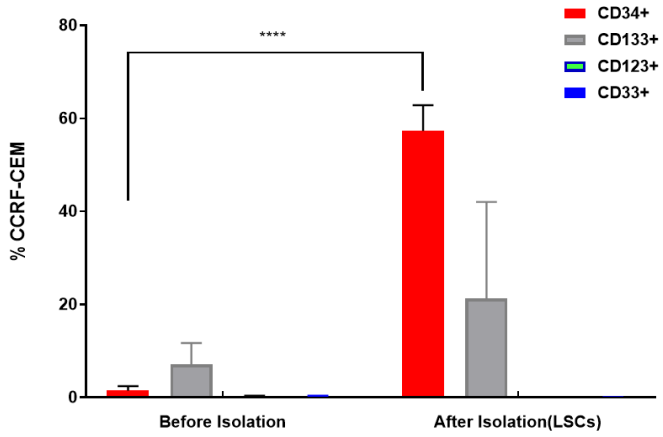


Figure 1. Percentage of CCRF-CEM cells before and after isolation (CCRF-CEM CD34+ cells considered as Leukemia Stem Cells, LSCs). The graph illustrates the expression levels of CD34+, CD133+, CD123+, and CD33+ markers in CCRF-CEM cells before isolation and after the enrichment of CD34+ cells. Statistical significance between the groups is indicated (****p < 0.0001).

3.2. Evaluation of Cellular Viability

Based on the data from Figure 2, the evaluation of CCRF-CEM CD34+ stem cell line showed that at low concentrations (10 - 40 µg) after 24 hours of treatment, cell viability increased compared to the control group, but the change was not statistically significant. After 48 hours of treatment, cell viability at these concentrations (10 - 40 µg) was significantly increased compared to the control (a: *p < 0.05, b: **p < 0.01). At 72 hours, cell viability also increased compared to the control group, with a statistically significant increase observed particularly at the 40 µg dose (b: **p < 0.01). At higher concentrations (80 - 320 µg), cell proliferation continued to increase across all time points. Specifically, at doses of 80 - 160 µg, significant increases in cell viability were observed at 48 and 72 hours compared to the control. At the highest concentration (160 µg), cell proliferation showed a statistically significant increase across all time points (c: ***p < 0.001, d: ****p < 0.0001).

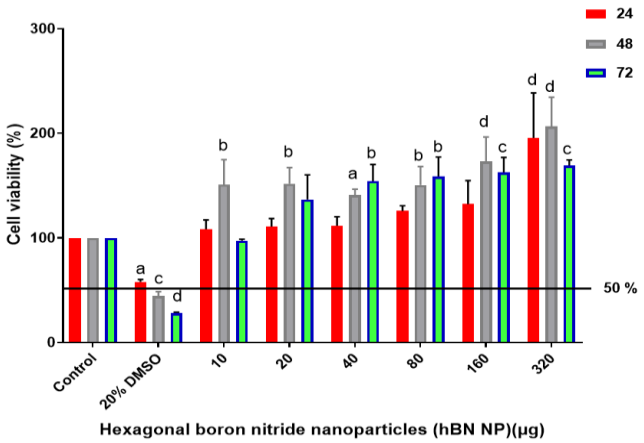


Figure 2. This bar graph illustrates the impact of various concentrations of hBN NP on CCRF-CEM 34+ cell viability, measured at different time points (24, 48, and 72 hours). The x-axis represents the doses of hBN NP used, given in microgram (µg) units, while the y-axis shows the percentage of cell viability compared to the control group. The error bars represent the standard deviation of the mean. The experiments were performed in triplicate. The horizontal dashed line indicates 50% cell viability. DMSO 20% was used as a positive control. Different concentrations are compared with the control group and significant differences are shown with other letters (a: *p < 0.05, b: **p < 0.01, c: ***p < 0.001, d: ****p < 0.0001).

Figure 3. represents the effects of hBN NP on HL-60 cells. After 24 hours of treatment, a statistically significant increase in cell proliferation was observed at all concentrations (a: *p < 0.05, d: ****p < 0.0001). Additionally, a significant increase in cell proliferation was noted at high doses (8 and 10 µg) of hBN NP after 48 and 72 hours of treatment compared to the control group (a: *p < 0.05, b: **p < 0.01). No significant changes were observed at other concentrations and time points.

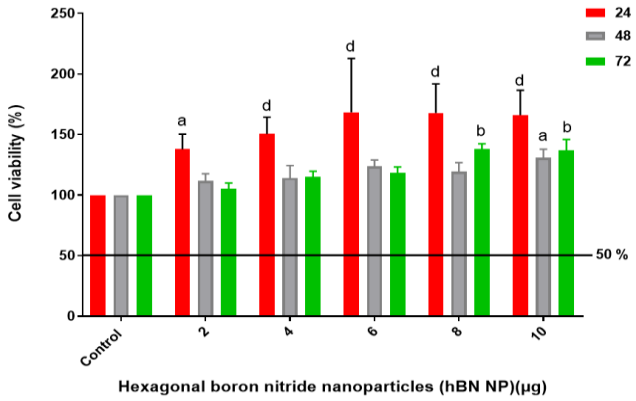


Figure 3. This bar graph illustrates the impact of various concentrations of hBN NP on HL-60 cell viability, measured at different time points (24, 48, and 72 hours). The x-axis represents the doses of hBN NP used, given in microgram (µg) units, while the y-axis shows the percentage of cell viability compared to the control group. The error bars represent the standard deviation of the mean. The experiments were performed in triplicate. The horizontal dashed line indicates 50% cell viability. Different concentrations are compared with the control group and significant differences are shown with other letters (a: *p < 0.05, b: **p < 0.01, d: ****p < 0.0001).

Figure 4. shows the effect of hBN NPs at various doses on the viability of healthy PBMNCs. A significant increase in cell viability was observed in healthy PBMNCs treated with hBN NPs at 6 and 10 µg concentrations for 48 hours compared to the control group (a: *p < 0.05, c: ***p < 0.001). No significant changes were observed at other concentrations and time points.

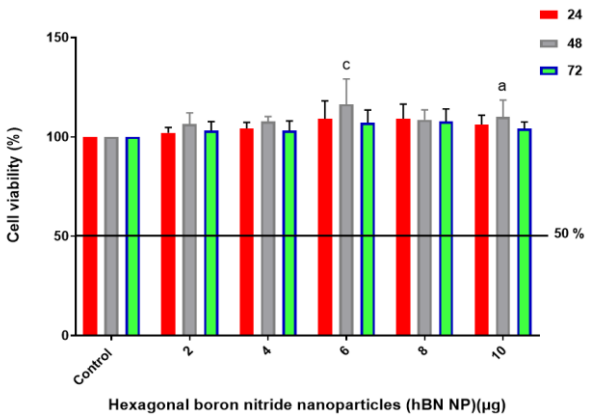


Figure 4. This bar graph illustrates the impact of various concentrations of hBN NP on healthy PBMNC viability, measured at different time points (24, 48, and 72 hours). The x-axis represents the doses of hBN NP used, given in microgram (µg) units, while the y-axis shows the percentage of cell viability compared to the control group. The error bars represent the standard deviation of the mean. The experiments were performed in triplicate. The horizontal dashed line indicates 50% cell viability. Different concentrations are compared with the control group and significant differences are shown with letters (a: *p < 0.05, c: ***p < 0.001).

4. Discussion

Identifying compounds that do not exhibit anticancer properties is critical for understanding the limitations of current cancer therapies and the underlying mechanisms of drug resistance. Studies have shown that various compounds are ineffective against cancer cells, highlighting the need for more targeted approaches in cancer treatment.

This study aimed to investigate the biological effects of hBN NPs on leukemia cancer cells and healthy cells to determine their potential therapeutic or adverse effects. The initial experiments focused solely on cell viability using MTS assays, which indicated that hBN NPs do not possess anticancer properties. As a result, no further investigations were pursued.

Leukemia stem cells are among the key factors influencing disease relapse and progression (25,26). Notably resistant to chemotherapy, these stem cells were exposed to high doses of hBN NPs. Despite the high dosage, a proliferative effect of hBN NPs was observed on CCRF-CEM CD34+ cells. One potential reason for this could be the activation of intracellular proliferation pathways, such as AKT/mTOR or MAPK signaling pathways, which may accelerate cell growth and division. One study found that one of the primary mechanisms by which boron affects cell proliferation is the phosphoinositide 3-kinase (PI3K)/AKT signaling pathway. Studies have shown that low doses of boron can increase the proliferation of intestinal epithelial cells by activating this pathway, which is crucial for cell growth and survival (27). This activation is believed to occur through boron's estrogen-like effects, particularly via the estrogen receptor ERβ; this further modulates mitochondrial apoptosis signaling pathways, promoting cell proliferation while inhibiting apoptosis (27,28).

Boron-containing nanoparticles have been investigated for their ability to stimulate mesenchymal stem cell (MSC) proliferation and differentiation. In particular, boron-doped hydroxyapatites have been shown to increase MSC adhesion and promote osteogenic differentiation, which is critical for bone tissue engineering (29,30). The presence of boron in these nanomaterials not only improves cell viability but also regulates the expression of key proteins involved in bone formation, such as collagen and osteocalcin (31,32)

An additional mechanism potentially underlying the proliferative effects of hBN nanoparticles may involve their ability to mitigate intracellular oxidative stress, thereby enhancing cellular survival capacity. Additionally, the maintenance of cancer stem cell viability might be attributed to the suppression of apoptotic pathways and the upregulation of anti-apoptotic genes, such as BCL-2, by hBN NPs. Furthermore, hBN NPs might support cell growth through their effects on the extracellular matrix or cell microenvironment. These findings suggest that hBN NPs may lack potential therapeutic effects on leukemia stem cells.

The absence of the expected cytotoxic effect and the continued viability of CCRF-CEM CD34+ cells following high-dose application of hBN NPs suggest that the cells may have triggered adaptive or stress

responses to the excessive doses. In such scenarios, cells can exhibit an enhanced protective or proliferative response to high doses, possibly leading to adaptive mechanisms such as the activation of antioxidant defense systems or cell signaling pathways. Based on this observation, we transitioned to low-dose applications of hBN NPs to allow for a more precise evaluation of their effects and to elucidate the dose-response relationship in the cells more clearly. The rationale for using lower doses on HL-60 cells was to observe more physiological effects and to establish a more consistent dose-response curve. Additionally, since high doses may exhibit non-toxic or even stimulatory effects on cells, we hypothesized that the expected cytotoxic effect might be more pronounced at lower doses. Therefore, we aimed to more accurately assess the sensitivity of cancer cells to treatment and to identify potential therapeutic ranges. However, we observed that hBN NPs similarly exhibited a proliferative effect on HL-60 cells. Possible reasons for this outcome may include the enhancement of cell proliferation through the modulation of intracellular signaling pathways, such as PI3K/AKT and mTOR, the insufficient promotion or absence of ROS production, the increased expression of anti-apoptotic proteins (e.g., Bcl-2), or the reduction in the activity of pro-apoptotic proteins (e.g., Bax, Bak).

The interaction of boron nanoparticles with cellular pathways can also affect the expression of anti-apoptotic genes. Studies have shown that boron-containing compounds can induce the expression of genes that promote cell survival and inhibit those that lead to apoptosis (33). This dual effect promotes cell proliferation and increases cancer cells' resistance to therapeutic interventions. Additionally, hBN NPs might accelerate the cell cycle in leukemia cells by influencing proteins that regulate the cell cycle, such as cyclins and CDKs. Therefore, further research is needed to comprehensively study the biological effects of hBN NPs and assess their suitability for cancer treatment.

Consistent with our findings, a similar study demonstrated that pravastatin, a cholesterol-lowering drug, is ineffective in reducing the growth of neuroblastoma cells in culture. This observation aligns with previous research showing that open-ring statins like pravastatin do not exhibit significant anticancer activity, unlike their closed-ring counterparts (34). These results indicate that the structural characteristics of these compounds play a crucial role in their biological activity against cancer cells.

Moreover, drug resistance remains a significant obstacle in cancer treatment. It is well established that chemotherapy agents, such as paclitaxel, initially kill cancer cells but eventually become ineffective due to the development of chemotherapy resistance (35). This resistance can be attributed to various factors, including genetic mutations and alterations in drug metabolism, which limit the efficacy of many anticancer agents. The inability of some compounds to maintain effectiveness against evolving cancer cell populations underscores the importance of ongoing research into alternative therapeutic strategies.

The role of the tumor microenvironment in drug resistance cannot be overlooked. It has been noted that the microenvironment of solid tumors can hinder the penetration of anticancer drugs, thereby reducing their efficacy (36). This limitation is further complicated by the heterogeneity of cancer cell populations within tumors, which can exhibit varying sensitivities to treatment (37–39)

There is an increasing need for selective anticancer agents that can effectively target malignant cells without affecting normal cells (40). The narrow therapeutic window of many current treatments often results in significant side effects, highlighting the need to identify compounds that, although lacking inherent anticancer properties, can serve as adjuvants in combination therapies or enhance the efficacy of more potent agents. In our observations, hBN NPs did not demonstrate significant toxicity toward healthy cells, as evidenced by the lack of a meaningful reduction in cell viability. In cancer treatment, the ideal agents are those that can selectively target cancer cells while sparing healthy cells. The lack of toxicity of hBN NPs in healthy cells is crucial for potential therapeutic applications, as it suggests that the compound might affect only cancer cells while preserving healthy cells. The minimal toxicity of hBN NPs to healthy cells also implies a reduced inflammatory response, which could help prevent systemic toxicity and inflammatory complications. The biocompatible and biostable properties of hBN NPs may further support tissue regeneration and repair by interacting favorably with cells. Their ineffectiveness on healthy cells could be advantageous for maintaining tissue integrity. Given these positive attributes, further studies should explore the effects of hBN NPs on cancer cells, particularly in solid tumors, to

assess their broader therapeutic potential. Boron has also been shown to significantly affect cardiac myocytes. Studies have shown that boron increases DNA synthesis and facilitates cell cycle entry in cardiomyocytes, indicating its potential role in cardiac regeneration after injury (41). This regenerative capacity is further supported by findings that boron promotes the expression of growth factors and cytokines necessary for tissue repair and regeneration (29,42)

Boron also plays a role in immune cell proliferation. For example, it has been observed that boron can induce lymphocyte proliferation and regulate macrophage responses that are vital for immune function. The interaction of boron with certain biological ligands and stabilizing macromolecular complexes may contribute to these immunological effects by enhancing the overall immune response (43)

The findings suggest that boron-based hBN NPs exhibit proliferative effects on leukemia cancer cells and stem cells, indicating that they may not be suitable for leukemia treatment. Our results demonstrate that leukemia cancer cells develop resistance to hBN NPs treatment, which limits the impact of the treatment on the cells and reduces its therapeutic efficacy. Studies on leukemia and other resistant cancer types indicate that the reasons for the lack of response to treatment are associated with various factors, including genetic and epigenetic alterations, cell cycle regulation, disruption of apoptotic mechanisms, and non-drug-related mechanisms (44,45).

The use of hBN NPs in combination with other therapeutic agents could enable the development of novel treatment strategies that may alter the response of cancer cells to therapy. Combination therapies involving different nanoparticles or chemotherapeutic drugs can exhibit synergistic or additive effects in cancer cells, potentially targeting resistance mechanisms and enhancing therapeutic efficacy. Therefore, it is recommended to expand the scope of studies involving boron nanoparticles and test them on other cell lines. Future studies using various leukemia cell lines and stem cell models could provide insights into how and under what conditions resistance to treatment develops, guiding the development of targeted therapeutic strategies against these resistance mechanisms.

REFERENCES

1. Shroff GS, Truong MT, Carter BW, Benveniste MF, Kanagal-Shamanna R, Rauch G, et al. Leukemic Involvement in the Thorax. Radiogr Rev Publ Radiol Soc N Am Inc. 2019;39(1):44–61.
2. Saraswati E. Leukemia: AML, CML, ALL and CLL. [cited 2024 Sep 14]; Available from: https://www.academia.edu/23210507/Leukemia_AML_CML_ALL_and_CLL
3. Dadwal A, Baldi A, Kumar Narang R. Nanoparticles as carriers for drug delivery in cancer. Artif Cells Nanomedicine Biotechnol. 2018;46(sup2):295–305.
4. Lacouture M, Sibaud V. Toxic Side Effects of Targeted Therapies and Immunotherapies Affecting the Skin, Oral Mucosa, Hair, and Nails. Am J Clin Dermatol. 2018 Nov;19(Suppl 1):31–9.
5. Khademi R, Mohammadi Z, Khademi R, Saghazadeh A, Rezaei N. Nanotechnology-based diagnostics and therapeutics in acute lymphoblastic leukemia: a systematic review of preclinical studies. Nanoscale Adv. 2023;5(3):571–95.
6. Krishnan V, Rajasekaran AK. Clinical nanomedicine: a solution to the chemotherapy conundrum in pediatric leukemia therapy. Clin Pharmacol Ther. 2014 Feb;95(2):168–78.
7. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2021 Feb;20(2):101–24.
8. Ihsanullah I. Boron nitride-based materials for water purification: Progress and outlook. Chemosphere. 2021 Jan 1;263:127970.
9. Pan D, Su F, Liu H, Ma Y, Das R, Hu Q, et al. The Properties and Preparation Methods of Different Boron Nitride Nanostructures and Applications of Related Nanocomposites. Chem Rec N Y N. 2020 Sep 22;20.
10. Türkez H, Arslan ME, Sönmez E, Açikyildiz M, Tatar A, Geyikoğlu F. Synthesis, characterization and cytotoxicity of boron nitride nanoparticles: emphasis on toxicogenomics. Cytotechnology. 2019 Feb;71(1):351–61.
11. Li X, Zhi C, Hanagata N, Yamaguchi M, Bando Y, Golberg D. Boron nitride nanotubes functionalized with mesoporous silica for intracellular delivery of chemotherapy drugs. Chem Commun. 2013 Jul 23;49(66):7337–9.
12. Sharker SM. Hexagonal Boron Nitrides (White Graphene): A Promising Method for Cancer Drug Delivery. Int J Nanomedicine. 2019 Dec 19;14:9983–93.
13. Ailuno G, Balboni A, Caviglioli G, Lai F, Barbieri F, Dellacasagrande I, et al. Boron Vehiculating Nanosystems for Neutron Capture Therapy in Cancer Treatment. Cells. 2022 Dec 13;11(24):4029.

14. Barth RF, Mi P, Yang W. Boron delivery agents for neutron capture therapy of cancer. Cancer Commun Lond Engl. 2018 Jun 19;38(1):35.
15. Nakamura H, Koganei H, Miyoshi T, Sakurai Y, Ono K, Suzuki M. Antitumor effect of boron nitride nanotubes in combination with thermal neutron irradiation on BNCT. Bioorg Med Chem Lett. 2015 Jan 15;25(2):172–4.
16. Wang W, Lin J, Xing C, Chai R, Abbas S, Song T, et al. Fe3O4 nanoparticle-coated boron nitride nanospheres: Synthesis, magnetic property and biocompatibility study. Ceram Int. 2017 Jun 1;43(8):6371–6.
17. Niskanen J, Zhang I, Xue Y, Golberg D, Maysinger D, Winnik FM. Boron nitride nanotubes as vehicles for intracellular delivery of fluorescent drugs and probes. Nanomed. 2016;11(5):447–63.
18. Weng Q, Wang B, Wang X, Hanagata N, Li X, Liu D, et al. Highly water-soluble, porous, and biocompatible boron nitrides for anticancer drug delivery. ACS Nano. 2014 Jun 24;8(6):6123–30.
19. Zhang H, Feng S, Yan T, Zhi C, Gao XD, Hanagata N. Polyethyleneimine-functionalized boron nitride nanospheres as efficient carriers for enhancing the immunostimulatory effect of CpG oligodeoxynucleotides. Int J Nanomedicine. 2015 Aug 24;10:5343–53.
20. Galanzha EI, Shashkov EV, Spring PM, Suen JY, Zharov VP. In vivo, noninvasive, label-free detection and eradication of circulating metastatic melanoma cells using two-color photoacoustic flow cytometry with a diode laser. Cancer Res. 2009 Oct 15;69(20):7926–34.
21. Nagrath S, Sequist LV, Maheswaran S, Bell DW, Irimia D, Ulkus L, et al. Isolation of rare circulating tumour cells in cancer patients by microchip technology. Nature. 2007 Dec;450(7173):1235–9.
22. Kar F, Söğüt I, Hacıoğlu C, Göncü Y, Şenturk H, Şenat A, et al. Hexagonal boron nitride nanoparticles trigger oxidative stress by modulating thiol/disulfide homeostasis. Hum Exp Toxicol. 2021 Sep;40(9):1572–83.
23. Meriç N, Albayrak E, Gülbaş Z, Kocabaş F. MEIS inhibitors reduce the viability of primary leukemia cells and Stem cells by inducing apoptosis. Leuk Lymphoma. 2024 Feb;65(2):187–98.
24. Turan RD, Albayrak E, Uslu M, Siyah P, Alyazici LY, Kalkan BM, et al. Development of Small Molecule MEIS Inhibitors that modulate HSC activity. Sci Rep. 2020 May 14;10(1):7994.
25. Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, et al. Drug Resistance in Cancer: An Overview. Cancers. 2014 Sep 5;6(3):1769–92.
26. Park NH, Cheng W, Lai F, Yang C, Florez de Sessions P, Periaswamy B, et al. Addressing Drug Resistance in Cancer with Macromolecular Chemotherapeutic Agents. J Am Chem Soc. 2018 Mar 28;140(12):4244–52.
27. Chen S, Huang J, Liu T, Zhang F, Zhao C, Jin E, et al. PI3K/Akt signaling pathway mediates the effect of low-dose boron on barrier function, proliferation, and apoptosis in rat intestinal epithelial cells. Sci Rep. 2024 Jan 3;14(1):393.
28. Jin E, Pei Y, Liu T, Ren M, Hu Q, Gu Y, et al. Effects of boron on the proliferation, apoptosis, and immune function of splenic lymphocytes through ERα and ERβ. Food Agric Immunol. 2019 Jan 1;30(1):743–61.
29. Ciftci E, Köse S, Korkusuz P, Timuçin M, Korkusuz F. Boron containing nano hydroxy apatites (B-N-HAp) Stimulate mesenchymal stem cell adhesion, proliferation and differentiation. [cited 2024 Oct 26];631. Available from: https://avesis.akdeniz.edu.tr/yayin/967192dd-d6e4-4fff-a4a9-0676830de93a/boron-containing-nano-hydroxy-apatites-b-n-hap-stimulate-mesenchymal-stem-cell-adhesion-proliferation-and-differentiation
30. Uysal İ, Yılmaz B, Evis Z. Boron doped hydroxapatites in biomedical applications. J Boron. 2020 Dec 29;5(4):199–208.
31. Hakki SS, Bozkurt BS, Hakki EE. Boron regulates mineralized tissue-associated proteins in osteoblasts (MC3T3-E1). J Trace Elem Med Biol Organ Soc Miner Trace Elem GMS. 2010 Oct;24(4):243–50.
32. Capati MLF, Nakazono A, Igawa K, Ookubo K, Yamamoto Y, Yanagiguchi K, et al. Boron Accelerates Cultured Osteoblastic Cell Activity through Calcium Flux. Biol Trace Elem Res. 2016 Dec;174(2):300–8.
33. Chen J, Yang Q, Liu M, Lin M, Wang T, Zhang Z, et al. Remarkable Boron Delivery Of iRGD-Modified Polymeric Nanoparticles For Boron Neutron Capture Therapy. Int J Nanomedicine. 2019 Oct 8;14:8161.
34. Kumar B, Cole WC, Prasad KN. Alpha tocopheryl succinate, retinoic acid and polar carotenoids enhanced the growth-inhibitory effect of a cholesterol-lowering drug on immortalized and transformed nerve cells in culture. J Am Coll Nutr. 2001 Dec;20(6):628–36.
35. Lee YH, Kim M, Park HJ, Park JY, Song ES, Lee H, et al. Chemical screening identifies the anticancer properties of Polyporous parvovarius. J Cancer. 2023;14(1):50–60.
36. Trédan O, Galmarini CM, Patel K, Tannock IF. Drug resistance and the solid tumor microenvironment. J Natl Cancer Inst. 2007 Oct 3;99(19):1441–54.
37. Ding L, Ley TJ, Larson DE, Miller CA, Koboldt DC, Welch JS, et al. Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. Nature. 2012 Jan;481(7382):506–10.
38. Genetic and epigenetic heterogeneity in cancer: a genome-centric perspective - PubMed [Internet]. [cited 2024 Sep 14]. Available from:

https://pubmed.ncbi.nlm.nih.gov/19441078/

39. Lambert G, Estévez-Salmeron L, Oh S, Liao D, Emerson BM, Tlsty TD, et al. An analogy between the evolution of drug resistance in bacterial communities and malignant tissues. Nat Rev Cancer. 2011 May;11(5):375–82.
40. Khazir J, Mir BA, Pilcher L, Riley DL. Role of plants in anticancer drug discovery. Phytochem Lett. 2014 Feb 1;7:173–81.
41. Bouchareb R, Katz M, Saadallah N, Sassi Y, Ali S, Lebeche D. Boron improves cardiac contractility and fibrotic remodeling following myocardial infarction injury. Sci Rep. 2020 Oct 13;10(1):17138.
42. Demirci S, Doğan A, Aydın S, Dülger EÇ, Şahin F. Boron promotes streptozotocin-induced diabetic wound healing: roles in cell proliferation and migration, growth factor expression, and inflammation. Mol Cell Biochem. 2016 Jun 1;417(1):119–33.
43. Routray I, Ali S. Boron Induces Lymphocyte Proliferation and Modulates the Priming Effects of Lipopolysaccharide on Macrophages. PloS One. 2016;11(3):e0150607.
44. Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. The Different Mechanisms of Cancer Drug Resistance: A Brief Review. Adv Pharm Bull. 2017 Sep;7(3):339–48.
45. Qiao H, Zhang L, Fang D, Zhu Z, He W, Hu L, et al. Surmounting tumor resistance to metallodrugs by co-loading a metal complex and siRNA in nanoparticles. Chem Sci. 2021 Apr 1;12(12):4547–56.

Osmangazi Journal of Med, 2025;47(1):32-
DOI: 10.20515/otd.1498328

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Challenges in Non-Invasive Ventilation: Understanding the Causes of NIV Failure and Complications

Noninvaziv Ventilasyondaki Zorluklar: NIV Başarısızlığı ve Komplikasyonlarının Nedenleri Anlamak

Erdem Yalçınkaya, Emel Eryüksel, Sait Karakurt, Hüseyin Arıkan, Umut Sabri Kasapoğlu, Sehnaz Olgun Yıldızeli

Pulmonary and Critical Care Department, Marmara University Pendik Training and Research Hospital, Istanbul, Türkiye

ORCID ID of the authors

EY. 0000-0002-1293-3719
EE. 0000-0002-2194-8066
SK. 0000-0002-6699-5798
HA. 0000-0001-8837-2527
SO. 0000-0002-3236-3995
USK. 0000-0003-2869-9872

Correspondence / Sorumlu yazar:
Erdem YALÇINKAYA
Pulmonary and Critical Care Department, Marmara University Pendik Training and Research Hospital, Istanbul, Türkiye

e-mail: drerdemyalcinkaya@gmail.com

Abstract: Non-invasive ventilation (NIV) has been successfully used in the treatment of acute respiratory failure. The objective of this study was to evaluate complications arising from NIV and their impact on therapy failure, with a specific focus on identifying the most common NIV-related complication leading to NIV failure. A retrospective analysis was conducted on data from 99 patients (54 males, mean age 66 +/- 8 years) who were admitted to Internal Intensive Care Unit between January 1, 2015, and December 30, 2017. These patients received NIV due to acute respiratory failure and were monitored in the intensive care unit for more than 24 hours. The patients' demographic data, causes of acute respiratory failure, and NIV-related complications were obtained from the recorded data. Complications with NIV included discomfort, which developed in 21 patients (21%); air leakage observed in 18 patients (18%), skin erosion in 16 patients (16%), irritated and dry eyes in 9 patients (9%), skin ulcer in 5 patients (5%), abdominal tension in 3 patients (3%), claustrophobia in 2 patients (2%), and hypotension in 1 patient (1%). Univariate and multivariate analyses conducted to evaluate the factors associated with NIV failure showed that discomfort with NIV was the most common factor contributing to failure (p = 0.039). Discomfort as an NIV-related complication was identified as the main factor of failure. Choosing the right equipment, providing appropriate ventilatory support, and thorough monitoring are key to minimizing complications and maximizing the effectiveness of NIV therapy.
Keywords: Non-Invasive Ventilation, Complications, Discomfort, Treatment Failure

Özet: Non-invaziv ventilasyon (NIV), akut solunum yetmezliğinin tedavisinde başarılı bir şekilde kullanılmaktadır. Bu çalışmanın amacı, NIV uygulamasına bağlı gelişen komplikasyonları ve bu komplikasyonların tedavi başarısızlığı üzerindeki etkilerini değerlendirmek olup, özellikle NIV başarısızlığına en sık neden olan komplikasyonu belirlemeye odaklanılmıştır. 1 Ocak 2015 ile 30 Aralık 2017 tarihleri arasında Dahili Yoğun Bakım Ünitesine kabul edilen 99 hastanın (54 erkek, ortalama yaş 66 +/- 8 yıl) verileri üzerine retrospektif bir analiz yapıldı. Bu hastalara, akut solunum yetmezliği nedeniyle NIV uygulandı ve 24 saati aşan süre boyunca yoğun bakım ünitesinde takip edildiler. Hastaların demografik verileri, akut solunum yetmezliği nedenleri ve NIV komplikasyonları kaydedilen verilerden elde edildi. NIV ile ilişkili komplikasyonlar arasında 21 hastada (%21) gelişen rahatsızlık, 18 hastada (%18) hava kaçağı, 16 hastada (%16) cilt erozyonu, 9 hastada (%9) gözlerde iritasyon ve kuruluk, 5 hastada (%5) cilt ülseri, 3 hastada (%3) abdominal gerginlik, 2 hastada (%2) klostrofobi ve 1 hastada (%1) hipotansiyon yer almaktaydı. NIV başarısızlığı ile ilişkili faktörleri değerlendirmek amacıyla yapılan univaryant ve multivaryant analizlerde, NIV kullanımına bağlı rahatsızlık, başarısızlığa en sık katkıda bulunan faktör olarak tespit edilmiştir (p = 0,039). Bu çalışmada, NIV ile ilişkili bir komplikasyon olarak rahatsızlık, başarısızlığın ana faktörü olarak belirlenmiştir. Doğru ekipmanın seçilmesi, uygun ventilatuvar desteğin sağlanması ve titiz izlem, komplikasyonların en aza indirilmesi ve NIV tedavisinin etkinliğinin artırılması için önemlidir.
Anahtar Kelimeler: Non-İnvaziv Ventilasyon, Komplikasyonlar, Rahatsızlık, Tedavi Başarısızlığı

Ethics Committee Approval: This study was designed and conducted in accordance with the ethical guidelines set forth in the Declaration of Helsinki, and the study protocol was approved by the Marmara University Clinical Researches Ethics Committee

(Date: 08.12.2017, Decision No:09.2017.746

).**Informed Consent:** This study did not require informed consent.

Authorship Contributions:

Copyright Transfer Form: Copyright Transfer Formwas signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that thisstudy received no financial support.

Received : 09.06.2024

Accepted : 26.11.2024

Published : 28.11.2024

How to cite/ Atıf için: Yalçınkaya E, Eryüksel E, Karakurt S, Arıkan H, Kasapoglu US, Olgun Yıldızeli S, Challenges in Non-Invasive Ventilation: Understanding the Causes of NIV Failure and Complications, Osmangazi Journal of Medicine, 2025;47(1):

1. Introduction

The term non-invasive ventilation (NIV) refers to the application of ventilation without any direct airway access, meaning without the use of an endotracheal or tracheostomy tube[1]. NIV has been used for over 25 years in the treatment of respiratory failure, with its indications continuously expanding and the list of contraindications steadily decreasing [2]. It is widely accepted as an effective treatment for acute respiratory failure, particularly in cases associated with chronic obstructive pulmonary disease (COPD) and acute cardiogenic pulmonary edema[3-6]. Increasingly, more data and efficacy studies are emerging on the use of NIV for other conditions associated with acute respiratory failure. NIV has been shown to reduce the need for intubation, shorten hospital stays, and decrease both morbidity and mortality [7-9].

Successful endpoints are only achieved by appropriate patient selection and tolerance of NIV. The occurrence of pain, pressure sores, agitation, stress, discomfort, or claustrophobia leads to low tolerance and thereby acceptance of NIV [10]. The acceptance of NIV could be related to the patient-device interface and accompanying air leak, the severity of disease condition, agitation, and the mode as well as settings of NIV being used.

NIV failure, defined as the need for endotracheal intubation, the failure rate of NIV varies from 5% to 40% [8, 11, 12]. Studies have identified several factors influencing failure, patient discomfort or rejection[10, 13, 14] including the underlying disease [14, 15], baseline arterial blood gas values and severity of the condition [16], the experience of the team administering NIV, and the equipment used [17].

NIV is generally a safe treatment method, with most complications being minor and related to the mask. Major complications are rare [18].

The number of studies comparing the impact of complications arising during NIV on the failure is limited. The objective of this retrospective cross-sectional study was to determine the complications in subjects who underwent NIV in our center and evaluate the impact of complications on the failure of NIV.

2. Materials and Methods

This was a retrospective cross-sectional study conducted between January 2015 and December 2017. We retrospectively included subjects aged 18 years or older who were admitted to our 12-bed internal intensive care unit (ICU) with acute respiratory failure and underwent NIV. Since this was a retrospective analysis based on patient records, informed consent was not required. The study protocol was approved by the institutional ethics committee (Approval date: 20.09.2017, No: 746).

NIV was initiated in accordance with the clinical protocols of the ICU at that time, for patients who met one or more of the following criteria: hypercapnia ($PaCO_2$ > 45 mm Hg) with pH < 7.35, hypoxemia (PaO_2/FiO_2 < 200), respiratory rate > 25/min despite normal blood gas parameters, or use of accessory respiratory muscles.

NIV failure was defined by the need for endotracheal intubation [12]. Indications for emergency intubation included respiratory or cardiac arrest, unconsciousness, agitation unresponsive to sedation, massive aspiration, inability to clear secretions, heart rate < 50 with impaired consciousness, or hemodynamic instability unresponsive to fluids and vasoactive agents [19].

Patients were intubated due to NIV failure if they exhibited one or more of the following: an increase in $PaCO_2 \geq 10$ mm Hg and a decrease in pH ≥ 0.10; PaO_2 < 60 mm Hg or SaO_2 < 90% despite high FiO_2; tachypnea, use of accessory respiratory muscles, thoracoabdominal paradox, inability to protect the airway, excessive pulmonary secretions, or altered mental status[20, 21] Conventional intensive care ventilators were used throughout the study period.

In this retrospective study, according to the clinical protocol, NIV had been interrupted every 4 hours for facial and oral care. Arterial blood gases had been measured 1 hour after the initiation of NIV and then twice daily or when clinically indicated. Respiratory patterns, consciousness, and vital signs had been continuously monitored throughout the treatment.

The selection of oronasal or full-face masks (Respironics, Inc.) was made based on clinical practices in place during the study period. An appropriately sized mask was chosen based on the patient's facial type. However, records on the number of patients and the type of interface used were not available. Initial NIV settings included an inspiratory pressure of 10 cm H_2O and an end-expiratory pressure of 5 cm H_2O, which was adjusted to achieve a tidal volume of at least 5 ml/kg

and a respiratory rate below 25/min. FiO_2 was titrated to maintain an oxygen saturation of at least 90%. Subjects who had been receiving bronchodilator therapy continued to do so via nebulization. Oral feeding was permitted after the first 24 hours unless contraindicated.

Demographic data, causes of acute respiratory failure, arterial blood gas tensions at the initiation of NIV and NIV-related complications were collected from the patients' medical records. Based on the outcomes and records, complications of non-invasive ventilation (NIV) were categorized under the following groups: discomfort, skin erosion, air leakage, hypotension, skin ulceration, eye irritation, abdominal distension, and claustrophobia.

Discomfort in NIV refers to the physical and psychological strain caused by factors such as mask type, strap tightness, and airflow pressure, often reducing patient tolerance and potentially leading to NIV failure [22].

Statistical Analysis

SPSS 21.0 Statistics Software Program was used for analysis of the study results. We used Pearson Chi-square test and Fisher's exact tests and Mann-Whitney U Tests for univariate analysis of risk factors. A multivariate logistic regression analysis was used to assess the significant factors from univariate analysis. Pearson Chi-square test and risk analysis were carried out to evaluate the relationship between mortality and achievement. The results were evaluated at a confidence interval of 95% and a significance level of $p<0,05$.

3. Results

Nearly 500 patients were admitted to the ICU over the two-year period. Of these, the study included a total of 99 subjects who were admitted with respiratory failure from various causes and received NIV. The demographic characteristics of 99 subjects are shown in (Table 1).

NIV was administered to 52 patients (52%) for COPD, 13 patients (13%) for acute pulmonary edema associated with congestive heart failure, 25 patients (25%) for pneumonia, and 9 patients (9%) for other reasons.

NIV failure was observed in 25 patients (25%). Discomfort related to NIV developed in 21 patients (21%), while air leaks were documented in 18 patients (18%), skin erosion in 16 patients (16%), irritated and dry eyes in 9 patients (9%), skin ulcers in 5 patients (5%), abdominal tension in 4 patients (4%), and claustrophobia in 2 patients (2%). (Table 2).

The univariate and multivariate analyses showed that discomfort to NIV was significantly effective in the failure of NIV (p=0,039) (Table 2 and Table 3). Furthermore, while all subjects successfully treated with NIV were discharged from the hospital, the mortality rate was 64% among those who failed NIV (Table 4). Of the 99 patients who received NIV, 83 were discharged.

Table 1. Demographic characteristics and indications for the use of NIV in patients

Patients	
Sex (Female/Male) (n)	45/54
Age (year)	66+/-8
Exacerbation in COPD (n)	52
Pneumonia (n)	25
Acute Cardiogenic Pulmonary Edema (n)	13
Obesity Hypoventilation Syndrome (OHS) (n)	4
Neuromuscular Diseases (n)	3
Asthma (n)	2

Table 2. Complications Associated with Failure and Success (Univariate Chi-square analysis)

		Failure		Success		p
		n	%	n	%	
Presence of complications	No	11	24,4%	34	75,6%	X^2=0,029 p=0,527
	Yes	14	25,9%	40	74,1%	
Discomfort	No	16	20,5%	62	79,5%	X^2=4,376 p=0,039
	Yes	9	42,9%	12	57,1%	
Skin Erosion	No	22	26,5%	61	73,5%	X^2=0,428 p=0,380
	Yes	3	18,8%	13	81,2%	
Air Leakage	No	22	27,5%	59	72,5%	X^2=0,908 p=0,264
	Yes	3	16,7%	15	83,3%	
Hypotension	No	24	24,5%	74	75,5%	X^2=2,990 p=0,253
	Yes	1	100,0%	0	0,0%	
Skin Ulcer	No	24	25,5%	70	74,5%	X^2=0,077 p=0,627
	Yes	1	20,0%	4	80,0%	
Eye irritation	No	23	25,6%	67	74,4%	X^2=0,048 p=0,593
	Yes	2	22,2%	7	77,8%	
Abdominal distension	No	24	25,3%	71	74,7%	X^2=0,000 p=0,736
	Yes	1	25,0%	3	75,0%	
Clauostrophobia	No	24	24,7%	73	75,3%	X^2=0,662 p=0,443
	Yes	1	50,0%	1	50,0%	

Table 3. Factors Associated with Failure (Multivariate Logistic Regression Analysis)

				95% C.I.for OR	
	B	p	OR	Lower	Upper
Hypoxemic Respiratory Failure	-1,531	0,008	4,62	1,50	14,25
Discomfort	-2,062	0,002	141,52	2,07	29,91
Constant – model constant	2,094	0,000	8,12		

Table 4. Relationship Between Mortality and Failure

(Chi-Square and Risk Analysis)

		Discharged		Ex		p
		n	%	n	%	
	Failed	9	36,0%	16	64,0%	X^2=56,490 p=0,000
	Successfully treated	74	100,0%	0	0,0%	

4. Discussion

Our study demonstrated that discomfort related to NIV, along with other complications such as air leaks, skin erosion, and claustrophobia, was a significant factor contributing to the failure of non-invasive ventilation. This finding provides valuable insights into the critical role that patient tolerance and the management of NIV-related side effects play in determining the success of NIV treatment. Additionally, the study underscores the significant difference in outcomes, with a high mortality rate among patients who experienced NIV failure, highlighting the importance of developing better strategies to improve patient comfort with NIV therapy.

NIV failure is influenced by several factors, including delayed initiation of NIV, inappropriate ventilation pressures, limited experience of the clinical team, and, most importantly, the patient's clinical condition.

In our study all patients who were successfully treated with NIV were discharged from the hospital, while those who experienced NIV failure had an ICU mortality rate of 64%, consistent with findings from the study by Demoule et al.[23].

Although NIV is generally considered more comfortable for patients than invasive mechanical ventilation (IMV), discomfort can affect as many as 30–50% of patients. Despite the best efforts of skilled caregivers, discomfort remains a contributing factor in 12-33% of NIV failures [24-26]. In our study, discomfort related to NIV was observed in 21 patients (21%).

Discomfort during NIV is often related to the device and the ventilation modality used [24]. Among various types of NIV masks, tolerance is lowest for the mouthpiece, followed by nasal and oronasal masks [27]. All attachment systems are considered to cause varying levels of discomfort on the skin, and tightening the straps to reduce air leaks and improve patient-ventilator synchrony can further decrease tolerance [27]. In some cases, switching to a different strap system or mask may be necessary to alleviate discomfort [28]. Helmets tend to be better tolerated than masks, leading to longer usage and a lower NIV failure rate [29]. However, some studies have reported similar comfort levels between the two interfaces or even greater discomfort with the helmet [30].

Discomfort has been identified as a key factor in failed NIV application [31]. Exploring solutions to reduce discomfort may enhance the success of this treatment method.

Air leakage from the mask was identified as one of the factors leading to failure in a multi-center prospective study by Carlucci et al.[10]. In our study, air leakage from the mask was observed in 18% of the patients. Other studies have reported air leak rates as high as 50% [28, 32]. The lower incidence of air leakage in our study may be attributed to the careful selection of the most appropriate masks before initiating NIV.

In selected patients, and when clinical status allows, a trial of high-flow nasal cannula (HFNC) oxygen therapy can be considered as an alternative in cases of intolerance to the various interfaces used for NIV [33].

The ventilator machine is obviously important during NIV. Consistent with recent findings [34], asynchrony events are significantly reduced when using a dedicated NIV ventilator compared to ICU ventilators with an NIV algorithm. This is likely due to the dedicated ventilator's more efficient and specialized system for compensating air leaks [35]. Various strategies can help reduce discomfort during NIV, including the use of ventilators with air-leak detection and compensation algorithms, implementing leak-insensitive ventilation modes, lowering the applied pressure, and selecting the appropriate interface [36].

Moreover, even though sedation is not mandatory during NIV therapy, the addition of a small amount of analgosedation like dexmedetomidine may help selected patients to better tolerate NIV, which can help to achieve the desired outcomes. A systematic review found that using sedative and analgesic drugs, particularly dexmedetomidine, during NIV can enhance clinical outcomes in patients with acute respiratory failure. Dexmedetomidine was shown to be superior to other sedatives in improving certain clinical parameters and increasing patient compliance with NIV. However, it is essential to closely monitor patients' vital signs to ensure the safe administration of these drugs and optimize the effectiveness of NIV therapy [37].

In a retrospective study on patients who received NIV after extubation and had discomfort to NIV interface in seven intensive care units (ICUs),

sedation and/or analgesia were used in 41 out of 80 patients (analgesia in 17, sedation in 11, and both in 13) at some time during NIV therapy. Those who received sedation and/or analgesia showed reduced NIV failure rate (15 vs 38%, p = 0.015), mortality (7 vs 33%, p = 0.004), and length of ICU stay after extubation [38]. In our study, no sedative agents were used in patients undergoing NIV. The high rate of NIV failure due to discomfort observed in our study may be one of the contributing factors.

To date, there are no principles or algorithms to guide the use of sedation during NIV [39]. Observational studies and clinical trials have explored the potential use of sedatives or analgesics to alleviate patient discomfort and address or prevent NIV intolerance. However, there is insufficient strong evidence to establish a standardized guideline, and the selection of drugs is largely guided by the physician's clinical judgment and preference. [40].

Our study has two primary limitations. Firstly, it was a single-center study, and secondly, data collection was restricted to patient records**.**

5. Conclusion

In conclusion, to achieve the best patient outcomes, NIV should be administered by a skilled and experienced team. Proper patient selection, guided by clinical judgement and existing protocols, is crucial, especially when considering factors that increase the risk of NIV failure. Continuous monitoring is essential, particularly in an ICU or step-down unit, until the patient is stabilized. This should include not only tracking vital signs and gas exchange but also ensuring patient comfort, managing air leaks, and optimizing patient-ventilator interaction. Choosing the right equipment, providing appropriate ventilatory support, and thorough monitoring are key to minimizing complications and maximizing the effectiveness of NIV therapy

REFERENCES

1. Ramakrishnan, N., et al., Guidelines for noninvasive ventilation in acute respiratory failure. Indian journal of critical care medicine, 2010. 10(2): p. 117-147.
2. Chawla, R., et al., ISCCM guidelines for the use of non-invasive ventilation in acute respiratory failure in adult ICUs. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine, 2020. 24(Suppl 1): p. S61.
3. Lightowler, J.V., et al., Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. Bmj, 2003. 326(7382): p. 185.
4. Masip, J., et al., Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. Jama, 2005. 294(24): p. 3124-3130.
5. Osadnik, C.R., et al., Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews, 2017(7).
6. Aliberti, S., et al., A real life evaluation of non invasive ventilation in acute cardiogenic pulmonary edema: a multicenter, perspective, observational study for the ACPE SIMEU study group. BMC emergency medicine, 2018. 18: p. 1-5.
7. Brochard, L., et al., Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. New England Journal of Medicine, 1995. 333(13): p. 817-822.
8. Çelikel, T., et al., Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. Chest, 1998. 114(6): p. 1636-1642.
9. Navarra, S.M., M.T. Congedo, and M.A. Pennisi, Indications for non-invasive ventilation in respiratory failure. Reviews on recent clinical trials, 2020. 15(4): p. 251-257.
10. Carlucci, A., et al., Noninvasive versus conventional mechanical ventilation: an epidemiologic survey. American journal of respiratory and critical care medicine, 2001. 163(4): p. 874-880.
11. Nava, S. and P. Ceriana, Causes of failure of noninvasive mechanical ventilation. Respiratory care, 2004. 49(3): p. 295-303.
12. Ozyilmaz, E., A.O. Ugurlu, and S. Nava, Timing of noninvasive ventilation failure: causes, risk factors, and potential remedies. BMC pulmonary medicine, 2014. 14: p. 1-10.
13. Kim, T., et al., Utilization of pain and sedation therapy on noninvasive mechanical ventilation in Korean intensive care units: a multi-center prospective observational study. Acute and Critical Care, 2020. 35(4): p. 255-262.
14. Thille, A.W., et al., Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. Critical Care, 2013. 17: p. 1-8.
15. Antonelli, M., et al., Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive care medicine, 2001. 27: p.

1718-1728.
16. Meduri, G.U., et al., Noninvasive positive pressure ventilation via face mask: first-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. Chest, 1996. 109(1): p. 179-193.
17. Carlucci, A., et al., Changes in the practice of non-invasive ventilation in treating COPD patients over 8 years. Intensive care medicine, 2003. 29: p. 419-425.
18. Cammarota, G., R. Simonte, and E. De Robertis, Comfort during non-invasive ventilation. Frontiers in Medicine, 2022. 9: p. 874250.
19. Ferrer, M., et al., Noninvasive ventilation during persistent weaning failure: a randomized controlled trial. American journal of respiratory and critical care medicine, 2003. 168(1): p. 70-76.
20. Esteban, A., et al., Noninvasive positive-pressure ventilation for respiratory failure after extubation. New England Journal of Medicine, 2004. 350(24): p. 2452-2460.
21. Epstein, S.K. and R.L. Ciubotaru, Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. American journal of respiratory and critical care medicine, 1998. 158(2): p. 489-493.
22. Carron, M., et al., Complications of non-invasive ventilation techniques: a comprehensive qualitative review of randomized trials. British journal of anaesthesia, 2013. 110(6): p. 896-914.
23. Demoule, A., et al., Benefits and risks of success or failure of noninvasive ventilation. Intensive care medicine, 2006. 32: p. 1756-1765.
24. Nava, S. and N. Hill, Non-invasive ventilation in acute respiratory failure. The Lancet, 2009. 374(9685): p. 250-259.
25. Cuvelier, A., et al., Cephalic versus oronasal mask for noninvasive ventilation in acute hypercapnic respiratory failure. Intensive care medicine, 2009. 35: p. 519-526.
26. Conti, G., et al., Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. Intensive care medicine, 2002. 28: p. 1701-1707.
27. Fraticelli, A.T., et al., Physiological effects of different interfaces during noninvasive ventilation for acute respiratory failure. Critical care medicine, 2009. 37(3): p. 939-945.
28. Gay, P.C., Complications of noninvasive ventilation in acute care. Respiratory care, 2009. 54(2): p. 246-258.
29. Chiumello, D., et al., Noninvasive positive pressure ventilation delivered by helmet vs. standard face mask. Intensive care medicine, 2003. 29: p. 1671-1679.
30. Racca, F., et al., Effectiveness of mask and helmet interfaces to deliver noninvasive ventilation in a human model of resistive breathing. Journal of Applied physiology, 2005. 99(4): p. 1262-1271.
31. Grieco, D.L., et al., Non-invasive ventilatory support and high-flow nasal oxygen as first-line treatment of acute hypoxemic respiratory failure and ARDS. Intensive care medicine, 2021. 47: p. 851-866.
32. Hill, N.S., Problems, remedies, and strategies to optimize the success of noninvasive ventilation. Noninvasive Positive Pressure Ventilation: Principles and Applications. Hill NS (Ed). Armonk, NY, Futura Publishing, 2001: p. 187-213.
33. Tan, D., et al., High-flow nasal cannula oxygen therapy versus non-invasive ventilation for chronic obstructive pulmonary disease patients after extubation: a multicenter, randomized controlled trial. Critical Care, 2020. 24: p. 1-10.
34. Carteaux, G., et al., Patient-ventilator asynchrony during noninvasive ventilation: a bench and clinical study. Chest, 2012. 142(2): p. 367-376.
35. Leone, M., et al., Noninvasive respiratory support in the hypoxaemic peri-operative/periprocedural patient: a joint ESA/ESICM guideline. Intensive care medicine, 2020. 46: p. 697-713.
36. Cammarota, G., et al., New setting of neurally adjusted ventilatory assist during noninvasive ventilation through a helmet. Anesthesiology, 2016. 125(6): p. 1181-1189.
37. Yang, B., L. Gao, and Z. Tong, Sedation and analgesia strategies for non-invasive mechanical ventilation: A systematic review and meta-analysis. Heart & Lung, 2024. 63: p. 42-50.
38. Ni, Y.-N., et al., The effect of sedation and/or analgesia as rescue treatment during noninvasive positive pressure ventilation in the patients with Interface intolerance after Extubation. BMC Pulmonary Medicine, 2017. 17: p. 1-9.
39. Longrois, D., et al., Sedation in non-invasive ventilation: do we know what to do (and why)? Multidisciplinary respiratory medicine, 2014. 9: p. 1-8.
40. Hilbert, G., P. Navalesi, and C. Girault, Is sedation safe and beneficial in patients receiving NIV? Yes. 2015, Springer. p. 1688-1691.

Osmangazi Journal of Med, 2025;47(1):39-48
DOI: 10.20515/otd.1562220

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Extra-thyroidal Cancers in Euthyroid Hashimoto's Patients Under Levothyroxine Treatment: Outlook A Single Tertiary Center Cases

Levotiroksin Tedavisi Alan Ötiroid Hashimoto Hastalarında Tiroid Dışı Kanserler: Tek Bir Tersiyer Merkezin Hastalarına Bakış

Havva Sezer

Department of Internal Medicine, Division of Endocrinology, Koç University School of Medicine, Istanbul, Türkiye

ORCID ID of the authors

HS. 0000-0002-2730-7307

Correspondence / Sorumlu yazar:
Havva SEZER
Address/ Adres: Department of Internal Medicine, Division of Endocrinology, Koç University School of Medicine, Istanbul, Türkiye
e-mail: hasezer@kuh.ku.edu.tr

Ethics Committee Approval: This study was designed and conducted in accordance with the ethical guidelines set forth in the Declaration of Helsinki, and the study protocol was approved by the Koc University Biomedical Researche Ethics Committee

Date: 25.03.2024, Decision No: 2024.136.IRB2.061

Informed Consent: This study did not require informed consent.

Authorship Contributions: HS.

Copyright Transfer Form: Copyright Transfer Formwas signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that thisstudy received no financial support.

Received : 06.10.2024

Accepted : 26.11.2024

Published : 28.11.2024

Abstract: We aimed to investigate the frequency of extra-thyroidal cancer (ETC) in euthyroid Hashimoto's patients under levothyroxine (LT4) treatment. Moreover, we determined whether cancer development could be related to demographic, clinical, biochemical, and metabolic parameters. Consecutive participants in the follow-up above 18 years old diagnosed with hypothyroidism caused by Hashimoto's thyroiditis (HT) in a single tertiary center between 2016 December and 2023 December were included in the study. A total of 577 Hashimoto's patients were analyzed retrospectively. The study population was divided into two subgroups according to presence or absence of ETC. Demographic, clinical, biochemical, and metabolic parameters were compared in patients with and without cancer. Mean age was 52.6±13.5 years. Of the 577 patients, 87.3% were female and 12.7% were male. The most prevalent two comorbidities accompanying HT were metabolic syndrome (36.4%) and obesity (31.2%). The frequency of concomitant appearance of ETC with HT was 13.3%. The most common two cancers were breast (46.2%) and ovary (8.7%). In multivariate analysis, older age (OR 1.030, 95% CI 1.012-1.049, p=0.001), positive family history for cancer (OR 1.859, 95% CI 1.117-3.092, p=0.017), and elevated fasting blood glucose (OR 1.022, 95% CI 1.007-1.037, p=0.005) were found to be significantly positively correlated with increased risk of cancer. This study revealed that the frequency of ETC was 13.3% in euthyroid Hashimoto's patients under LT4 treatment. Breast cancer was the most common cancer affecting study population. Older age, positive family history for cancer and elevated fasting blood glucose were defined as independent risk factors for cancer development.
Keywords: Hashimoto's thyroiditis, hypothyroidism, extra-thyroidal cancers

Özet: Levotiroksin (LT4) tedavisi alan ötiroid Hashimoto hastalarında tiroid dışı kanser (TDK) sıklığını araştırmayı amaçladık. Ayrıca kanser gelişiminin demografik, klinik, biyokimyasal ve metabolik parametrelerle ilişkili olup olmadığını da belirledik. Aralık 2016 ile Aralık 2023 tarihleri arasında tek bir tersiyer merkezde Hashimoto tiroiditi (HT) kaynaklı hipotiroidi tanısı alan 18 yaş üzeri takipteki ardışık katılımcılar çalışmaya dahil edildi. Toplam 577 Hashimoto hastası retrospektif olarak analiz edildi. Çalışma popülasyonu TDK olup olmamasına göre iki alt gruba ayrıldı. Kanserli ve kansersiz hastalarda demografik, klinik, biyokimyasal ve metabolik parametreler karşılaştırıldı.Bulgular: Ortalama yaş 52,6±13,5 yıldı. Beş yüz yetmiş yedi hastanın %87,3'ü kadın, %12,7'si erkekti. HT'ne eşlik eden en sık iki komorbidite metabolik sendrom (%36,4) ve obezite (%31,2) idi. HT ile TDK'in birlikte görülme sıklığı %13,3 idi. En sık görülen iki kanser meme (%46,2) ve over (%8,7) oldu. Çok değişkenli analizde, ileri yaşın (OR 1,030, %95 CI 1,012-1,049, p=0,001), pozitif aile öyküsünün (OR 1,859, %95 CI 1,117-3,092, p=0,017) ve yüksek açlık kan şekerinin (OR) 1,022, %95 CI 1,007-1,037, p=0,005) artan kanser riski ile anlamlı pozitif korelasyona sahip olduğu bulunmuştur. Bu çalışma, LT4 tedavisi alan ötiroid Hashimoto hastalarında TDK sıklığının %13,3 olduğunu ortaya çıkardı. Meme kanseri, çalışma popülasyonunu etkileyen en yaygın kanserdi. İleri yaş, pozitif aile öyküsü ve yüksek açlık kan şekeri, kanser gelişimi için bağımsız risk faktörleri olarak tanımlandı.
Anahtar Kelimeler: Hashimoto tiroiditi, hipotiroidi, tiroid dışı kanserler

How to cite/ Atıf için: Sezer H, Extra-thyroidal Cancers in Euthyroid Hashimoto's Patients Under Levothyroxine Treatment: Outlook A Single Tertiary Center Cases, Osmangazi Journal of Medicine, 2025;47(1):39-48

1. Introduction

Various risk factors increase the risk of cancer including family history, genetic mutations, environmental effects, and aging. Low-grade chronic inflammatory condition caused by impaired function of T cells may be also associated with the increased risk of certain types of cancer in different autoimmune disorders [1-4]. Hashimoto's thyroiditis (HT) is the most common autoimmune disease caused by hypothyroidism, which presents lymphocytic infiltration of thyroid gland and elevated autoantibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TgAb). In the literature, the link between HT and papillary thyroid cancer (PTC) was mainly assessed. There were many fine-needle aspiration cytology (FNAC) studies and archival thyroidectomy specimen studies [5,6]. FNAC studies show no significant correlation, whereas many of thyroidectomy specimen studies report a positive correlation [5]. A meta-analysis showed that PTC was more often found in patients with HT than in patients without HT [6]. However, there was a significant heterogeneity among the studies such as different study methods and different patient selection criteria [6]. Therefore, the relationship between HT and PTC has been controversial for decades. On the other hand, the number of studies investigating the link between HT and extra-thyroidal cancer (ETC) is limited [2,7]. A meta-analysis demonstrated that patients with HT had increased risk of developing various types of ETC when compared to people without HT [2]. People with under the effect of chronic inflammatory state are more prone to have several types of ETC, such as breast, liver, colon, bladder, prostate, stomach, ovarian, and skin cancers [3].

The exact mechanisms behind carcinogenesis in patients with HT are still unclear, but there are several hypotheses. Chronic inflammation induced by anti-thyroid antibodies plays an essential role in promoting tumorigenesis. Inflammatory cells release reactive oxygen species (ROS), inflammatory cytokines/chemokines, and growth factors in a chronic inflammatory microenvironment [3]. Oxidative stress causes deoxyribonucleic acid (DNA) damage and induces cell proliferation [3]. Proteins and lipids are damaged by ROS, resulting in their dysfunction [8]. In addition, DNA methylation occurs in tumor suppressor genes. It seems that genetic alterations and molecular abnormalities play a major role in inflammation-induced tumor development [8,9]. Inflammatory microenvironment also leads to angiogenesis, formats new blood vessels, and causes tumor aggressiveness [1]. The thyroid gland and neoplastic organ cells present several structural similarities [10,11]. Cross-reactivity of TPO antibodies with some antigens such as lactoperoxidase and myeloperoxidase may also cause destruction of cells and cancer development [10,11]. The increased expression of the sodium iodide symporter, and thyroid hormone receptors in both thyroid and various other extra-thyroidal tissues could play a role in the relationship between these two diseases [12,13]. Iodination of proteins initiates oxidative stress and may stimulate transformation of normal cells to cancer cells [10]. Cancer development and progression may be also associated with thyroid hormone status. Despite experimental clinical studies, there is contradictory evidence of the relationship between HT and risk of developing malignancy.

Diabetes mellitus (DM) is an important risk factor for developing many types of cancer [14-16]. Cancer development in patients with DM is associated with hyperglycemia, hyperinsulinemia, obesity, and dyslipidemia. These metabolic disorders cause a low-activity chronic inflammatory state and increase oxidative stress [14,15,17]. Hence, they may increase the many types of cancer initiation and progression. Furthermore, patients at pre-diabetes levels have increased risk for cancer development [18]. The relationships between these metabolic disorders and ETC are still unclear in patients with HT.

The aim of this present study was to investigate the frequency of ETC in euthyroid Hashimoto's patients under levothyroxine (LT4) treatment. Moreover, we analyzed whether cancer development could be related to clinical, biochemical, and metabolic parameters.

2. Materials and Methods

Ethical committee approval for this present retrospective cohort study was obtained on March 25, 2024, with decision number 2024.136.IRB2.061. The study was carried out according to the Declaration of Helsinki. Consecutive patients in the follow-up above 18 years old diagnosed with primary hypothyroidism caused by HT in a single tertiary center between 2016 December and 2023 December were included in the study. All patients were in euthyroid status under LT4 treatment.

HT was defined in presence of autoantibodies for either TPO, Tg or both. The positivity of antibodies was verified on two separate measurements for each patient at our single center. Furthermore, thyroid ultrasonography (USG) examination was performed to accurate chronic thyroiditis. The diagnosis of HT was made by roughness of the thyroid parenchyma, hypoechoic, and heterogenous thyroid structure at USG examination. Excluded were patients with <18 years old, pregnancy, breastfeeding, history for Graves' disease, HT in euthyroid status without taking LT4 treatment, serum negative autoimmune thyroiditis, history for subacute thyroiditis, human immunodeficiency virus disease, immune checkpoint inhibitor-induced thyroid dysfunction, taking immunomodulator medications, amiodarone, and lithium. There were 577 patients with eligibility criteria.

Characteristics of the subjects including age, gender, body mass index (BMI), history of smoking, family history for cancer in first degree relatives, presence of ETC, ETC localizations, time of cancer occurrence either before or after the diagnosis of HT, duration of hypothyroidism (years), daily LT4 dose to achieve euthyroid status (mcg), concurrent comorbid diseases [obesity, type 2 diabetes mellitus (T2DM), metabolic syndrome, and type 1 diabetes mellitus (T1DM)], laboratory findings [(fasting blood samples for TPOAb, TgAb, thyroid stimulating hormone (TSH), free T4 (FT4), glucose, and estimated glomerular filtration rate (eGFR), low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG), alanine aminotransferase enzyme (ALT), and 25-hydroxyvitamin D (25OHD)] were reviewed. eGFR was calculated by using Chronic Kidney Disease Epidemiology Collaboration equation. The National Cholesterol Education Programs Treatment Panel III (NCEP ATP III) criteria was used to define metabolic syndrome [19]. Demographic, clinical, biochemical, and radiological findings were obtained from the medical records.

Patients were divided into two subgroups according to presence or absence of ETC. Cancer group was compared to non-cancer group in terms of demographic, clinical, and biochemical parameters.

Assays

Serum TPOAb, TgAb, TSH, FT4, and 25OHD measurements were performed by using electrochemiluminescence immunoassay method. Positive TPOAb was defined as higher than 35 IU/mL and positive TgAb was defined as higher than 115 IU/mL. The minimum and maximum detectable TgAb concentrations were 10 IU/mL and 4000 IU/mL respectively. The minimum and maximum detectable TPOAb concentrations were 9 IU/mL and 600 IU/mL respectively. Enzymatic tests were used to measure serum glucose, LDL, and TG concentrations. Serum HDL level was measured by using a colorimetric assay system. The assessment of ALT enzyme activity was performed by using the International Federation of Clinical Chemistry method. Roche Cobas 503 PRO analyzer device was used for analysis of biochemical parameters. Immunochemistry tests were performed by using Roche Cobas 801 PRO module.

Statistical Analysis

IBM SPSS Statistics (version 28.0, Chicago, USA) program was used for data analysis. Descriptive statistics of variables were defined as percentage (%), frequency, mean±standard deviation, and median. A comparative analysis of independent groups studied by quantitative characteristics was performed using the Mann-Whitney U test. The Chi-Square test was used in the comparison of independent groups by qualitative characteristics. If the Chi-Square test did not meet the criteria Fisher's Exact test was used. The relationship of potential risk factors for the presence of ETC was evaluated by using logistic regression model. Odds ratios (OR) along with the 95% confidence intervals were calculated for predictors of ETC presence. The statistical significance level was defined when the p value was <0.05.

3. Results

This retrospective present study included 577 euthyroid patients with HT under LT4 treatment. Five hundred four (87.3%) patients were female, and 73 (12.7%) patients were male. Mean age was 52.6±13.5 years. Mean BMI was 27.2±4.7 kg/m^2. Of the 577 patients, 159 (27.6%) were smoking. Seventy seven (13.3%) patients had ETC. The results are summarized in Table 1. There were double cancers in 3 patients. A total of 80 malignant tumors were found: 37 (46.2%) were breast cancer, 7 (8.7%) were ovary cancer, 6 (7.5%) were leukemia, 5 were (6.2%) colon cancer, 4 (5%) were pancreas cancer, 3 (3.8) were bladder cancer, 3 (3.8%) were lung cancer, 3 (3.8%) were endometrial cancer, 2 (2.5%) were kidney cancer, and 2 (2.5%) were lymphoma. The remaining 8 (10%) patients had other cancer types: 1 prostate cancer, 1 malign melanoma, 1 testis cancer, 1 parotid cancer, 1 nasopharyngeal cancer, 1 cervix cancer, 1 stomach

cancer, and 1 laryngeal cancer. The classification of ETC types is shown in Table 2. In addition, there were 6 patients (1%) diagnosed with PTC through FNAC in our study population. The mean age at diagnosis for ETC was 50.9±12.8 years. Approximately, 55% of the patients were diagnosed with ETC after the diagnosis of HT. There was a positive family history for cancer in 146 (25.3%) patients. The most prevalent two comorbidities accompanying HT were metabolic syndrome (36.4%) and obesity (31.2%). Mean duration of hypothyroidism was 10.9±7.6 years. Mean daily LT4 dose to achieve euthyroidism was 77.2±35.2 mcg. Median TPOAb and TgAb concentrations were 209.0 IU/mL and 195 IU/mL, respectively. Mean TSH level in euthyroid status was 2.23±1.22 µIU/mL.

Patients with ETC were compared to those without cancer. The results of patients with or without ETC are shown in Table 3. Mean age was significantly higher in patients with cancer (p=0.000). Individuals with a first-degree family history for cancer had a higher risk of developing cancer than those without a family history (p=0.007). Rate of T2DM was higher in patients who had cancer (p=0.027). Duration of hypothyroidism was longer in patients without cancer (p=0.028). The TgAb titers were higher in cancer group compared with the non-cancer group (p=0.036). People with cancer had significantly higher fasting blood glucose (FBG) concentrations than those without cancer (p=0.000). The comparison of patients with and without cancer showed that mean eGFR was significantly lower in cancer group (p=0.001). Mean serum TG levels were elevated in patients with cancer in comparison with subjects without cancer (p=0.046). Compared with cancer group, the mean 25OHD level was lower in non-cancer group (p=0.007).

As shown in Table 4, univariate and multivariate data analyses were performed to identify significant predictors of cancer development. Independent risk factors related to increased risk of cancer were older age (OR 1.030, 95% CI 1.012-1.049, p=0.001); positive family history for cancer (OR 1.859, 95% CI 1.117-3.092, p=0.017); and elevated fasting blood glucose (OR 1.022, 95% CI 1.007-1.037, p=0.005).

Table 1. Demographic, clinical, metabolic, and biochemical features of the study population

Parameters	**Total (n=577)**
Age, years, mean±SD	52.6±13.5
Gender, n (%)	
Female	504 (87.3)
Male	73 (12.7)
BMI, kg/m^2, mean±SD	27.2±4.7
Current smoker, n (%)	159 (27.6)
Cancer, n (%)	77 (13.3)
Age at diagnosis (cancer), years, mean±SD	50.9±12.8
Cancer diagnosis, n (%)	
Before HT	35 (45.5)
After HT	42 (54.5)
Positive family history for cancer, n (%)	146 (25.3)
Comorbid conditions, n (%)	
None	311 (53.9)
Metabolic syndrome	210 (36.4)
Obesity	180 (31.2)
T2DM	57 (9.9)
T1DM	16 (2.8)
Duration of hypothyroidism, years, mean±SD	10.9±7.6
Daily levothyroxine dose to achieve euthyroidism, mcg, mean±SD	77.2±35.2
TPOAb, IU/mL, median	209.0
TgAb, IU/mL, median	195.0
TSH, µIU/mL, mean±SD	2.23±1.22
FT4, ng/dL, mean±SD	1.26±0.21
FBG, mg/dL, mean±SD	101.0±14.6
eGFR, mL/min/1.73 m^2, mean±SD	95.7±20.9
LDL, mg/dL, mean±SD	135.6±39.6
HDL, mg/dL, mean±SD	59.8±15.0
TG, mg/dL, mean±SD	132.3±73.4
ALT, U/L, mean±SD	20.3±9.7

25OHD, ng/mL, mean±SD	34.1±14.5

HT: Hashimoto's thyroiditis, SD: standard deviation, BMI: body mass index, T2DM: type 2 diabetes mellitus, T1DM: type 1 diabetes mellitus, TPOAb: thyroid peroxidase antibody. TgAb: thyroglobulin antibody, TSH: thyroid stimulating hormone, FT4: free T4, FBG: fasting blood glucose, eGFR: estimated glomerular filtration rate, LDL: low density lipoprotein, HDL: high density lipoprotein, TG: triglyceride, ALT: alanine aminotransferase, 25OHD: 25-hydroxyvitamin D

Table 2. Classification of cancer types

Cancer locations	**80 malignant tumors in 77 patients, n (%)**
Breast	37 (46.2)
Ovary	7 (8.7)
Leukemia	6 (7.5)
Colon	5 (6.2)
Pancreas	4 (5)
Bladder	3 (3.8)
Lung	3 (3.8)
Endometrial	3 (3.8)
Kidney	2 (2.5)
Lymphoma	2 (2.5)
Others	8 (10)

Table 3. Demographic, clinical, biochemical, and metabolic characteristics of the patients with and without cancer

Parameters	**Without cancer (n=500)**	**With cancer (n=77)**	**P value**
Age, years, mean±SD	51.8±13.4	58.3±13.1	**0.000^{m}**
Gender, n (%)			
Female	436 (87.2)	68 (88.3)	0.785^{X2}
Male	64 (12.8)	9 (11.7)	
BMI, kg/m^2, mean±SD	27.2±4.6	27.4±4.9	0.918^{m}
Current smoker, n (%)	141 (28.2)	18 (23.4)	0.378^{X2}
Positive family history of cancer, n (%)	117 (23.4)	29 (37.7)	**0.007^{X2}**
Comorbid conditions, n (%)			
None	274 (54.8)	37 (48.1)	0.269^{X2}
Metabolic syndrome	177 (35.4)	33 (42.9)	0.205^{X2}
Obesity	158 (31.6)	22 (28.6)	0.593^{X2}
T2DM	44 (8.8)	13 (16.9)	**0.027^{X2}**
T1DM	12 (2.4)	4 (5.2)	0.164^{X2}
Duration of hypothyroidism, years, mean±SD	11.0±7.4	9.8±8.4	**0.028^{m}**
Daily levothyroxine dose to achieve euthyroidism, mcg, mean±SD	77.2±34.5	77.1±39.4	0.822^{m}
TPOAb, IU/mL, median	215.5	174.0	0.330^{m}
TgAb, IU/mL, median	184.0	261.0	**0.036^{m}**
TSH, µIU/mL, mean±SD	2.24±1.23	2.16±1.12	0.684^{m}
FT4, ng/dL, mean±SD	1.26±0.21	1.27±0.22	0.765^{m}
FBG, mg/dL, mean±SD	100.2±14.1	106.4±16.5	**0.000^{m}**
eGFR, mL/min/1.73 m^2, mean±SD	97.0±20.6	86.2±22.8	**0.001^{m}**
LDL, mg/dL, mean±SD	136.0±39.6	133.1±39.6	0.726^{m}
HDL, mg/dL, mean±SD	59.6±14.7	60.5±16.9	0.586^{m}
TG, mg/dL, mean±SD	130.9±73.1	141.0±74.8	**0.046^{m}**
ALT, U/L, mean±SD	20.1±9.6	21.8±10.4	0.084^{m}
25OHD, ng/mL, mean±SD	33.6±14.7	37.3±12.8	**0.007^{m}**

HT: Hashimoto's thyroiditis, SD: standard deviation, BMI: body mass index, T2DM: type 2 diabetes mellitus, T1DM: type 1 diabetes mellitus, TPOAb: thyroid peroxidase antibody. TgAb: thyroglobulin antibody, TSH: thyroid stimulating hormone, FT4: free T4, FBG: fasting blood glucose, eGFR: estimated glomerular filtration rate, LDL: low density lipoprotein, HDL: high density lipoprotein, TG: triglyceride, ALT: alanine aminotransferase, 25OHD: 25-hydroxyvitamin D. ^{m}Mann-Whitney U test / ^{X2}Chi-Square test (Fischer test)

Table 4. Logistic regression analysis of the variables associated with cancer development

Parameters	Univariate analysis			Multivariate analysis		
	OR	**95% Cl**	**P**	**OR**	**95% Cl**	**P**
Age	1.036	1.018-1.055	**0.000**	1.030	1.012-1.049	**0.001**
Positive family history of cancer	1.978	1.193-3.278	**0.008**	1.859	1.117-3.092	**0.017**
Duration of hypothyroidism	0.976	0.942-1.010	0.169			
T2DM	1.451	1.037-2.030	**0.030**			
TgAb	1.000	1.000-1.001	**0.010**			
FBG	1.025	1.010-1.039	**0.001**	1.022	1.007-1.037	**0.005**
eGFR	0.975	0.964-0.987	**0.000**			
TG	1.002	0.999-1.005	0.266			
25OHD	1.016	1.001-1.032	**0.040**			

OR: odds ratio, Cl: confidence level, HT: Hashimoto's thyroiditis, T2DM: type 2 diabetes mellitus, TgAb: thyroglobulin antibody, FBG: fasting blood glucose, eGFR: estimated glomerular filtration rate, TG: triglyceride, 25OHD: 25-hydroxyvitamin D

4. Discussion

This present retrospective cohort study included 577 euthyroid Hashimoto's patients under LT4 treatment showed that the frequency of concomitant appearance of ETC was 13.3%. The most common 3 concurrent cancers were breast (46.2%), ovary (8.7%), and leukemia (7.5%). In multivariate analysis, older age, positive family history for cancer, and elevated fasting blood glucose level were independently associated with the increased risk of cancer.

The average rate of PTC among patients with HT was 1.2% in FNAC studies and ranged from 27.5% to 40.1% in thyroidectomy studies [5,6]. Researchers predominantly show that PTC patients with HT had a better prognosis and a lower risk of recurrence than those without HT [20]. However, there is not enough available data whether the coexistence of HT impacts on ETC frequency, characteristics and prognoses. Based on the ETC in the literature, most studies evaluated a link between HT and breast cancer. A meta-analysis included 28 studies that demonstrated increased breast cancer development in patients with chronic autoimmune thyroid disorder [21]. Two studies confirmed increased cancer risk in patients with HT [22,23]. A recent meta-analysis showed that patients with HT had a significantly increased risk of several types of ETCs including breast, lung, urogenital, digestive system, and blood cancers [2]. The frequency of ETCs in patients with HT ranged from 2% to 11%, with a mean rate of 6.5% [2]. Increased cancer risk and incidence are still under debate in patients with HT. A study conducted by Sarlis et al. [24] showed no relationship between breast cancer and HT. Prinzi et al. [25] evaluated ETCs in women with different benign and malign thyroid diseases. The most common ETC was breast in their study population. However, they found that lack of thyroid autoimmunity was associated with increased risk of ETC development [25]. According to our center's experience, the frequency of ETC was 13.3%. Moreover, approximately half of the malignant tumors were observed in breast tissue followed by ovarian and bone marrow. There may be a link between HT and breast cancer. Increased breast and ovarian cancer development may be related to female gender preponderance in patients with all autoimmune diseases. It is considered that there is an association between various autoimmune diseases and hematological malignancies such as leukemia, Hodgkin/non-Hodgkin lymphoma and myeloma [26].The underlying mechanisms include genetic, environmental factors, medical treatments of autoimmune diseases, and irregular immune function [26]. The incidence of acute leukemia and chronic myeloid leukemia was significantly higher among patients with autoimmune diseases when compared to general population [26]. Furthermore, primary familial autoimmune disease was a possible etiological factor in childhood acute leukemia [27]. Although there is an increased association between Hashimoto/hypothyroidism and non-Hodgkin lymphoma [26], it is not clear whether there is a possible link between HT and leukemia. This issue needs to be further investigation with larger sample size prospective studies.

Chiappa C et al. [23] showed a significant association between HT and cancer diagnosed with younger than 45 years old in both women and men. The other study showed that there was a link between ETC development and chronic autoimmune thyroiditis, especially in patients at young age [25]. In contrast to these study results, Chen et al. [22] reported that older age was associated with higher cancer risk in Hashimoto's patients. We confirmed this data. The mean age at diagnosis for cancer was

nearly 51 years old in our study. Moreover, more than one-half of cases were diagnosed with cancer after the diagnosis of HT. Hence, we suggest that patients in follow-up with HT, especially after the age of 50 should be screened for the development of several cancer types.

There is limited available data for the relationship between ETC and family history of cancer in patients with HT. A study did not find a statistically significant association between breast cancer and family history [23]. There was a positive correlation between HT and presence of ETC in our present study. Hence, based on our study results, we think that Hashimoto's patients with a family history of cancer should be followed up more closely for certain cancer types.

Most studies in the literature explored TPOAb concentration in cancer patients with autoimmune thyroid disorders. Studies were especially conducted on patients with breast cancer [7]. Some authors reported that there was a stronger correlation between breast cancer risk and presence of thyroid autoimmunity [28]. According to a study's results, TPOAb and TgAb levels were significantly higher in patients with breast cancer than in control group [29]. Patients with TPOAb and/or TgAb positivity had an increased risk for several types of cancer, such as melanoma, breast cancer and hematological cancers [25]. In contrast, some studies found that patients with absence of thyroid autoimmunity revealed higher risk for all types of ETC [25]. Tosovic et al. [30] showed that women with high levels of TPOAb had low breast cancer risk. This issue is still under debate. In our present study, TgAb titers were higher in cancer group. However, when this data was analyzed using multivariate statistics, there was no correlation between TgAb and development of cancer.

Cancer development could be related to thyroid function tests. A study showed that thyroid hormone receptor expression altered in breast cancer patients [31]. Thyroid hormone may bind and stimulate estrogen receptor levels and estrogen production in breast cancer cells [31]. Thyroid hormones may also cause proliferative effects on breast cells [31], and they have important regulator effect on hematopoiesis [32]. Hypothyroidism was an independent risk factor for developing breast cancer in women [33]. Breast cancer risk may be associated with different nationalities or geographical areas in patients with hypothyroidism [34]. A meta-analysis reported decreased cancer risk in the European population, and similar cancer risk in the non-European population [34]. Hypothyroidism was associated with slightly increased gynecological cancer risk [35]. There is controversial data for colorectal cancer. An elevated risk of colorectal cancer was reported in patients with hypothyroidism [36]. Increased cancer risk may be related to gender [37]. Gastric cancer was associated with male gender in patients with hypothyroidism [37]. There are studies which found decreased cancer risk in patients with hypothyroidism [38-42]. Hypothyroidism was related to a lower risk of breast cancer [38], rectal cancer [39], lung cancer [40], prostate cancer [41], and hepatocellular cancer [42]. LT4 treatment was associated with a reduced risk of breast cancer [43] and colorectal cancer [44]. Wang et al. [45] found no association between endometrial cancer and autoimmune hypothyroidism. Breast and ovary cancers were the most frequent two cancer types in our cohort. These study results might be explained with female predominance and subsequent occurrence of estrogen-related cancers. We included euthyroid HT patients under LT4 therapy in this present study. We are closely monitoring the thyroid function tests to avoid under or over treatment. LT4 replacement may decrease the risk of other cancer types. We think that Hashimoto's patients should be followed up carefully to keep them in euthyroid status.

A large study included 159.033 patients demonstrated that patients with DM had a higher risk of several types of ETC such as esophagus, breast, lung, pancreas, liver, endometrium, and colon [15]. In addition, patients with T1DM have also increased risk for cancer development [16]. There is no available data for DM, DM-related diseases and their relationship with ETC development in patients with HT. Our study results indicated that the most common concurrent cancers were breast, ovary, leukemia, colon, and pancreas, respectively. The presence of T2DM was not associated with cancer development, however, FBG levels were significantly positively correlated with cancer development in our multivariate analysis data. Hence, we should give priority to early diagnosis of DM and focus on the management of hyperglycemia to prevent ETC in Hashimoto's patients.

It is known that there is potential relationship between obesity and autoimmunity [17]. Elevated expression of pro-inflammatory cytokines such as leptin may be main factor of occurrence of autoimmunity in obese people [17]. Waring et al. showed that hypothyroidism was associated with increased metabolic syndrome risk [46]. Hypothyroidism is also associated with obesity [47].

Obesity and metabolic syndrome are remarkably associated with insulin resistance. Hyperinsulinemia increases cancer risk via triggering pro-inflammatory pathways and mitogenic activity [14]. A study reported increased cancer risk at several anatomic sites, including esophagus (adenocarcinoma), stomach, breast, pancreas, gallbladder, liver, colon, corpus uteri, and kidney in overweight and obese patients [48]. In our present study, nearly one-third of the patients had either metabolic syndrome or obesity but there was no correlation between these two metabolic disorders and ETC development in patients with HT. Dyslipidemia described as elevated LDL cholesterol concentration, high serum TG concentration and low HDL cholesterol concentration were associated with different cancer types [49]. Lipotoxicity caused by increased levels of free fatty acids plays an essential role in the development of insulin resistance and DM. This hyperlipidemic environment supports cancer cell growth and survival [14]. However, we found no difference in terms of plasma cholesterol levels in euthyroid HT patients with and without cancer.

Our study had several limitations. It was a retrospective single center study with a small sample size. The absence of non-HT age- and gender-matched control group is the other limitation of our study. More prospective cohort studies involving large sample size, multiple geographical regions, multiple ethnicities, long-term follow-up, and control group are needed to clarify the relationship between HT and ETC occurrence or outcomes of the ETCs in Hashimoto's patients in the future. We think that our study results are important. Because we evaluated many risk factors related to cancer. According to our study results euthyroid HT patients had increased risk for certain types of cancer. Although genetic susceptibility could not be changed, early diagnosis may be possible with screening especially in patients with positive family history of cancer. The number of risk factors may be decreased with more tight glucose control. Our findings could be useful for early diagnosis for common malignancies in patients with HT. We suggest that patients with HT should be monitored closely especially in the presence of above mentioned risk factors.

In conclusion, it seems that euthyroid Hashimoto's patients under LT4 therapy are more prone to develop certain types of cancer. In our study, breast cancer was the main cancer type associated with HT. Older age, positive family history for cancer and elevated fasting blood glucose were defined as independent risk factors for cancer development in patients with HT.

REFERENCES

1. Malhab LJB, Saber-Ayad MM, Al-Hakm R, Nair VA, Paliogiannis P, Pintus G, et al. Chronic inflammation, and cancer: the role of endothelial dysfunction and vascular inflammation. Curr Pharm Des. 2021;27(18):2156-69.
2. Hu X, Wang X, Liang Y, Chen X, Zhou S, Fei W, et al. Cancer risk in Hashimoto's thyroiditis: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2022;13:937871.
3. Khandia R, Munjal A. Interplay between inflammation and cancer. Adv Protein Chem Struct Biol. 2020;119:199-245.
4. Giat E, Ehrenfeld M, Shoenfeld Y. Cancer and autoimmune diseases. Autoimmun Rev. 2017;16(10):1049-57.
5. Jankovic B, Le KT, Hershman JM. Clinical review: Hashimoto's thyroiditis and papillary thyroid carcinoma: is there a correlation. J Clin Endocrinol Metab. 2013;98(2):474-482.
6. Lai X, Xia Y, Zhang B, Li J, Jiang Y. A meta-analysis of Hashimoto's thyroiditis and papillary thyroid carcinoma risk. Oncotarget. 2017;8(37):62414-62424.
7. Giustarini E, Pinchera A, Fierabracci P, Roncella M, Fustaino L, Mammoli C, et al. Thyroid autoimmunity in patients with malignant and benign breast diseases before surgery. Eur J Endocrinol. 2006;154(5):645-9.
8. Murata M. Inflammation and cancer. Environ Health Prev Med. 2018;23(1):50.
9. Rokavec M, Öner MG, Hermeking H. Inflammation-induced epigenetic switches in cancer. Cell Mol Life Sci. 2016;73(1):23-39.
10. Fröhlich E, Wahl R. Thyroid autoimmunity: role of anti-thyroid antibodies in thyroid and extra-thyroidal diseases. Front Immunol. 2017;8:521.
11. Haapala AM, Hyöty H, Parkkonen P, Mustonen C, Soppi E. Antibody reactivity against thyroid peroxidase and myeloperoxidase in autoimmune thyroidits and systemic vasculitis. Scand J Immunol. 1997;46(1):78-85.
12. Tazebay UH, Wapnir IL, Levy O, Dohan O, Zuckier LS, Zhao QH, et al. The mammary gland iodine transporter is expressed during lactation and in breast cancer. Nat Med. 2000;6(8):871-8.
13. Davies TF. The thyrotrophin receptors spread

themselves around. J Clin Endocrinol Metabol. 1994;79(5):1232-3.
14. Rojas A, Schneider I, Lindner C, Gonzalez I, Morales MA. Association between diabetes and cancer. Current mechanistic insights into the association and future challenges. Mol Cell Biochem. 2023;478(8):1743-58.
15. Hu Y, Zhang X, Ma Y, Yuan C, Wang M, Wu K, et al. Incident type 2 diabetes duration and cancer risk: a prospective study in two US cohorts. J Natl Cancer Inst. 2021;113(4):381-9.
16. Zádori N, Szakó L, Váncsa S, Vörhendi N, Oštarijaš E, Kiss S, et al. Six autoimmune disorders are associated with increased incidence of gastric cancer: a systematic review and meta-analysis of half a million patients. Front Immunol. 2021;12:750533.
17. Gontarz-Nowak K, Szklarz M, Szychlińska M, Matuszewski W, Bandurska-Stankiewicz E. A brief look at Hashimoto's disease, adrenal incidentalomas, obesity, and insulin resistance-could endocrine disruptors be the other side of the same coin? Medicina (Kaunas). 2023;59(7):1234.
18. Supabphol S, Seubwai W, Wongkham S, Saengboonmee C. High glucose: an emerging association between diabetes mellitus and cancer progression. J Mol Med (Berl). 2021;99(9):1175-93.
19. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman CI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and prevention: National Heart, Lung, and Blood Institute; American heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5.
20. Yang Y, Liu J, Shi X, Wang M. Clinical and pathological characteristics of patients with papillary thyroid carcinoma coexisting with Hashimoto's thyroiditis: a retrospective cohort study. Cancer Control. 2023;30:10732748231199647.
21. Hardefeldt PJ, Eslick GD, Edirimanne S. Benign thyroid disease is associated with breast cancer: a meta-analysis. Breast Cancer Res Treat. 2012;133(3):1169-77.
22. Chen YK, Lin CL, Cheng FT, Sung FC, Kao CH. Cancer risk in patients with Hashimoto's thyroiditis: a nationwide cohort study. Br J Cancer. 2013;109(9):2496-2501.
23. Chiappa C, Rovera F, Rausei S, Del Ferraro S, Fachinetti A, Lavazza M, et al. Breast cancer and thyroid diseases: analysis of 867 consecutive cases. J Endocrinol Invest. 2017;40(2):179-184.
24. Sarlis NJ, Gourgiotis L, Pucino F, Tolis GJ. Lack of association between Hashimoto thyroiditis and breast cancer: a quantitative research synthesis. Hormones (Athens). 2002;1(1):35-41.
25. Prinzi N, Sorrenti S, Baldini E, De Vito C, Tuccilli C, Catania A, et al. Association of thyroid diseases with primary extra-thyroidal malignancies in women: results of a cross-sectional study of 6,386 patients. PLoS One. 2015;10(3):e0122958.
26. Hemminki K, Huang W, Sundquist J, Sundquist K, Ji J. Autoimmune diseases and hematological malignancies: exploring the underlying mechanisms from epidemiological evidence. Semin Cancer Biol. 2020;64:114-121.
27. Till M, Rapson N, Smith PG. Family studies in acute leukemia in childhood: a possible association with autoimmune disease. Br J Cancer. 1979;40(1):62-71.
28. Graceffa G, Scerrino G, Militello G, Laise I, Randisi B, Melfa G, et al. Breast cancer in previously thyroidectomized patients: which thyroid disorders are a risk factor? Futur Sci OA. 2021;7(5):FSO699.
29. Shi XZ, Jin X, Xu P, Shen HM. Relationship between breast cancer and levels of serum thyroid hormones and antibodies: a meta-analysis. Asian Pac J Cancer Prev. 2014;15(16):6643-7.
30. Tosovic A, Becker C, Bondeson AG, Bondeson L, Ericsson OB, Malm C, et al. Prospectively measured thyroid hormones and thyroid peroxidase antibodies relation to breast cancer risk. Int J Cancer. 2012;131(9):2126-33.
31. Silva JM, Domínguez G, González-Sancho JM, García CM, Silva J, García-Andrade C, et al. Expression of thyroid hormone receptor/erbA genes is altered in human breast cancer. Oncogene. 2002;21(27):4307-16.
32. Moskowitz C, Dutcher JP, Wiernik PH. Association of thyroid disease with acute leukemia. Am J Hematol. 1992;39(2):102-7.
33. Huang CH, Wei CJ, Chien TC, Kuo CW, Lin SH, Su YC, et al. Risk of breast cancer in females with hypothyroidism: a nationwide, population-based, cohort study. Endocr Pract. 2021;27(4):298-305.
34. Wang B, Lu Z, Huang Y, Li R, Lin T. Does hypothyroidism increase the risk of breast cancer: evidence from a meta-analysis. BMC Cancer. 2020;20(1):733.
35. Leung JH, Wang SY, Leung HW, Yu TS, Chan ALF. Hypothyroidism and hyperthyroidism related to gynecologic cancers: a nationwide population-based cohort study. Sci Rep. 2024;14(1):1892.
36. Rostkowska O, Spychalski P, Dobrzycka M, Wilczyński M, Łachiński AJ, Obołończyk Ł, et al. Effects of thyroid hormone imbalance on colorectal cancer carcinogenesis and risk- a systematic review. Endokrynol Pol. 2019;70(2):190-7.
37. Dore MP, Manca A, Alfonso Pensamiento MC, Delitala AP, Fanciulli G, Piana AF, et al. Male predominance of gastric cancer among patients with hypothyroidism from a defined geographic area. J Clin Med. 2020;9(1):135.
38. Søgaard M, Farkas DK, Ehrenstein V, Jørgensen JO, Dekkers OM, Sørensen HT. Hypothyroidism and hyperthyroidism and breast cancer risk: a

nationwide cohort study. Eur J Endocrinol. 2016;174(4):409-14.
39. L'Heureux A, Wieland DR, Weng CH, Chen YH, Lin CH, Lin TH, et al. Association between thyroid disorders and colorectal cancer risk in adult patients in Taiwan. JAMA Netw Open. 2019;2(5):e193755.
40. Liu W, Zhi FH, Zheng SY, Yang HS, Geng XJ, Luo HH, et al. Hypothyroidism reduces the risk of lung cancer through oxidative stress response and PI3K/Akt signaling pathway: an RNA-seq and Mendelian randomization study. Heliyon. 2023;9(12):e22661.
41. Mondul AM, Weinstein SJ, Bosworth T, Remaley AT, Virtamo J, Albanes D. Circulating thyroxine, thyroid-stimulating hormone, and hypothyroid status and the risk of prostate cancer. PLoS One. 2012;7(10):e47730.
42. Lu L, Wan B, Li L, Sun M. Hypothyroidism has a protective causal association with hepatocellular carcinoma: a two-sample Mendelian randomization study. Front Endocrinol (Lausanne). 2022;13:987401.
43. Weng CH, Okawa ER, Roberts MB, Park SK, Umbricht CB, Manson JE, et al. Breast cancer risk in postmenopausal women with medical history of thyroid disorder in the women's health initiative. Thyroid. 2020;30(4):519-30.
44. Boursi B, Haynes K, Mamtani R, Yang YX. Thyroid dysfunction, thyroid hormone replacement and colorectal cancer risk. J Natl Cancer Inst. 2015;107(6):djv084.
45. Wang B, Luo Y, Liu T, Xu S, Pei J, Liu J, et al. Assessment of bidirectional relationships between hypothyroidism and endometrial cancer: a two-sample Mendelian randomization study. Front Endocrinol (Lausanne). 2024;15:1308208.
46. Waring AC, Rodondi N, Harrison S, Kanaya AM, Simonsick EM, Miljkovic I, et al. Thyroid function and prevalent and incident metabolic syndrome in older adults: the Health, Ageing, and Body Composition Study. Endocrinol. 2012;76(6):911-8.
47. Park HK, Ahima RS. Endocrine disorders associated with obesity. Best Pract Res Clin Obstet Gynaecol. 2023;90:102394.
48. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, et al, International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer-viewpoint of the IARC working group. N Engl J Med. 2016;375(8):794-8.
49. Liu W, Chakraborty B, Safi R, Kazmin D, Chang CY, McDonnell DP. Dysregulated cholesterol homeostasis results in resistance to ferroptosis increasing tumorigenicity and metastasis in cancer. Nat Commun. 2021;12(1):5103.

Osmangazi Journal of Med, 2025;47(1):49- 60
DOI: 10.20515/otd.1523116

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Yetişkin Bireylerin Aterojenik Riskine Etki Eden Faktörlerinin Değerlendirilmesi ve Diyet Antioksidan Kapasite ile İlişkisinin İncelenmesi

Evaluation of Factors Affecting Atherogenic Risk in Adults and Its Relationship with Dietary Antioxidant Capacity

[1]Dilara Uğraşkan, [2]Hacı Ömer Yılmaz

[1]Üsküdar Üniversitesi, Beslenme ve Diyetetik Bölümü, İstanbul, Türkiye
[2]Bandirma Onyedi Eylül Üniversitesi, Beslenme ve Diyetetik Bölümü, Balıkesir, Türkiye
*Yüksek Lisans Tez Danışmanı

ORCID ID of the authors

DU. 0009-0005-4365-2396
HÖY. 0000-0003-4597-7758

Correspondence / Sorumlu yazar:
Dilara UĞRAŞKAN

Üsküdar Üniversitesi, Beslenme ve Diyetetik Bölümü, İstanbul, Türkiye

e-mail: dilaraugraskan@gmail.com

Etik Kurul Onayı: This study was designed and conducted in accordance with the ethical guidelines set forth in the Declaration of Helsinki, and the study protocol was approved by the Üskidar Üniversitesi Non-interventional Clinical Researches Ethics Committee (Date: 28.03.2023, Decision No:3)

Telif Hakkı Devir Formu: Tüm yazarlar tarafından Telif Hakkı Devir Formu imzalanmıştır.

Yazar Katkısı: Çalışmanın tasarımı Hacı Ömer Yılmaz ve Dilara Uğraşkan tarafından yapılmıştır. Dilara Uğraşkan verileri toplamış, Hacı Ömer Yılmaz ve Dilara Uğraşkan istatistiksel analizleri gerçekleştirmiş ve makaleyi yazmıştır. Hacı Ömer Yılmaz makaleyi gözden geçirmiş ve tartışmaya katkıda bulunmuştur. Her iki yazar da makaleyi okumuş ve onaylamıştır.

Çıkar Çatışması Beyanı: Yazarlar arasında herhangi birçıkar çatışması bulunmamaktadır.

Destek ve Teşekkür Beyanı: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received : 27.07.2024
Accepted :.06.12.2024
Published : 09.12.2024

Abstract: This study was conducted to evaluate the factors affecting the atherogenic risk of adult individuals and to examine the relationship with dietary antioxidant capacity. The study was conducted with 143 participants who applied to the diet outpatient clinic of a medical center between April and September 2023. The participants were divided into obese (BMI≥30 kg/m2) and non-obese (BMI<30 kg/m2) according to Body Mass Index (BMI), the questionnaire consisting of Socio-Demographic Characteristics Form, DASH Diet Quality (DASH-Q) Scale, International Physical Activity Questionnaire (IPAQ) Short Form, 24-Hour Food Consumption Record Form was applied face-to-face. Statistical analysis of the data obtained was performed using SPSS 25.0 program. BMI, waist circumference, low density lipoprotein cholesterol (LDL-C), triglycerides (TG), plasma atherogenic index (PAI), castelli risk index-1 (CRI-1) were higher and high density lipoprotein cholesterol (HDL-C) was lower in obese participants ($p<0.05$). The most common disease was thyroid diseases with a rate of 21%. The DASH-Q value of 50.7% of the obese participants was found to be medium-high, while the DASH-Q value of 66.7% of the non-obese participants was found to be low ($p<0.05$). DASH-Q value had no effect on atherogenic risk ($p>0.05$). The physical activity level of the participants had no effect on atherogenic risk ($p>0.05$). BMI and waist circumference, which are among the diagnostic criteria for obesity, were found to be effective in atherogenic risk ($p<0.05$). It was found that Oxygen radical absorbance capacity (ORAC) of non-obese participants was higher ($p>0.05$), but ORAC had no significant effect on atherogenic risk ($p>0.05$). Studies examining the relationship between ORAC and factors affecting atherogenic risk are limited in the literature. As a result of this study, it was found that obesity was the most influential factor on atherogenic risk, and although ORAC was lower in the presence of obesity and atherogenic risk, there was no statistically significant relationship between them.
Keywords: Antioxidant capacity, Antioxidants, Atherogenicity index, Castelli risk index, Cardiovascular Diseases, Obesity

Özet: Bu çalışma, yetişkin bireylerin aterojenik riskine etki eden faktörleri değerlendirmek ve bu risk ile diyet antioksidan kapasitesi arasındaki ilişkiyi incelemek amacıyla gerçekleştirilmiştir. Nisan-Eylül 2023 tarihleri arasında bir tıp merkezinin diyet polikliniğine başvuran 143 katılımcı ile yürütülen çalışmada, katılımcılar Beden Kütle İndeksi'ne (BKİ) göre obez (BKİ ≥ 30 kg/m²) ve obez olmayan (BKİ < 30 kg/m²) olarak iki gruba ayrılmıştır. Sosyo-Demografik Özellikler Formu, DASH Diyet Kalitesi (DASH-Q) Ölçeği, Uluslararası Fiziksel Aktivite Anketi (IPAQ) Kısa Formu ve 24 Saatlik Besin Tüketim Kaydı Formu'ndan oluşan anket, yüz yüze uygulanmıştır. Elde edilen veriler, SPSS 25.0 programı kullanılarak istatistiksel olarak analiz edilmiştir. Obez katılımcıların olmayanlara göre BKİ'si, bel çevresi, düşük yoğunluklu lipoprotein lolesterolü (LDL-K), trigliseridi (TG), Plazma Aterojenik İndeksi (PAI), Castelli Risk İndeksi-1'i (CRI-1) yüksek, yüksek yoğunluklu lipoprotein kolesterolü (HDL-K) düşük bulunmuştur ($p<0.05$). Obez katılımcıların %50,7'sinin DASH-Q değeri orta-yüksek seviyede bulunurken, obez olmayan katılımcıların %66,7'sinin DASH-Q değeri düşük olarak belirlenmiştir ($p<0.05$). Ancak, DASH-Q değerinin aterojenik risk üzerindeki etkisi anlamlı bulunmamıştır ($p>0.05$). Ayrıca, katılımcıların fiziksel aktivite düzeyinin de aterojenik risk üzerinde etkili olmadığı görülmüştür ($p>0.05$). Buna karşın, obezite tanı kriterlerinden BKİ ve bel çevresinin aterojenik riskte anlamlı bir etkiye sahip olduğu tespit edilmiştir ($p<0.05$). Obez olmayan katılımcıların diyet antioksidan kapasitesinin değerlendirildiği oksijen radikal absorbans kapasitesinin (ORAC) daha yüksek olduğu gözlenmiş ($p>0.05$), ancak ORAC'ın aterojenik riske anlamlı bir etkisinin olmadığı sonucuna ulaşılmıştır ($p>0.05$). Literatürde aterojenik riske etki eden faktörlerin ORAC ile ilişkisinin incelendiği çalışmalar sınırlıdır. Bu çalışmada ise obezitenin aterojenik riske en fazla etki eden faktör olduğu; obezite ve aterojenik riskin varlığında ORAC düzeylerinin daha düşük olmasına rağmen aralarında istatistiksel olarak anlamlı bir ilişki bulunmadığı belirlenmiştir.
Anahtar Kelimeler: Antioksidan Kapasite, Antioksidanlar, Aterojenite indeksi, Castelli risk indeksi, Kalp ve Damar hastalıkları, Obezite

How to cite/ Atıf için: Uğraşkan D, Yılmaz HÖ.,Yetişkin Bireylerin Aterojenik Riskine Etki Eden Faktörlerinin Değerlendirilmesi ve Diyet Antioksidan Kapasite ile İlişkisinin İncelenmesi, Osmangazi Journal of Medicine, 2025;47(1):49-60

1. Giriş

Kardiyovasküler hastalıklar kalp ve kan damarlarını etkileyen bir grup hastalıktır (1). Genellikle atardamarların içindeki yağ birikimi ile karakterize olan, ateroskleroz olarak da bilinen, aterojen oluşumu sebebiyle meydana gelmektedir (2). Dünya Sağlık Örgütü (DSÖ) verilerinde 2000 yılından 2020 yılına kadar dünya çapındaki ölümlerin en büyük nedeninin %16'lık oranla aterojen oluşumunun yol açtığı iskemik kalp hastalığı olduğu belirtilmektedir (3). Türkiye İstatistik Kurumu (TÜİK) 2019 verilerine göre Türkiye'de ölüm nedenlerinin başında dolaşım sistemi hastalıkları gelmektedir. Dolaşım sistemi hastalıklarının en yüksek oranı %39.1 ile iskemik kalp hastalıkları, ikinci en yüksek oranı ise %22.2 ile serebrovasküler hastalıklardır (4).

Aterojen oluşumu, arterlerde ve aortta, kan damarlarının daralmasından kaynaklanan kan akışının azalması ya da durması sonucu meydana gelmektedir. Yüksek miktarda okside olmuş düşük yoğunluklu lipoprotein kolesterol (LDL-K) ve oksidatif stres, endotel disfonksiyona sebep olur (5, 6). Endotel disfonksiyon, monositlerin ve T lenfositlerin endotel hücrelere tutunmasına neden olur (7, 8). Monositler makrofajlara dönüşür, çok sayıda köpük hücre üretilir ve aterosklerotik lezyon büyür. Arterlerde kolesterol birikimi aterosklerotik plak ve yağlı çizgi oluşumuna katkı sağlar. Atrosklerotik lezyonun ilerlemesi fibröz kapsül oluşumuna, makrofaj ölümlerine, damarlarda kalsifikasyona, inflamasyon ve oksidatif stresin artmasına yol açar. İnflamasyonla birlikte aterosklerotik plak patlar (9, 7).

Aterojeni etkileyen risk faktörleri arasında yer alan obezite, adipositlerin proinflamatuar adipokinleri salgılamasını sağlar. Bu durum dislipidemiyi, kan basıncını ve inflamasyonu artırır, aterojen oluşumunu kolaylaştırır (10, 11, 12). Aterojeni etkileyen risk faktörleri arasında yer alan dislipideminin yol açtığı lipit profilindeki olumsuz yöndeki değişiklik, bireylerin aterosklerotik komplikasyon risklerini artırmaktadır (13, 14, 15, 16). Aterojen oluşumu beslenme ve fiziksel aktiviteyle yakından ilişkili bir süreçtir (17). Yetersiz fiziksel aktivite ateroskleroz riskini artırmaktadır (18). Doymuş yağlar, basit şeker ve işlenmiş besinlerden zengin diyetler oksidatif stresin artmasına, oksidatif stresin artması ise endotel disfonksiyona ve ateroskleroza neden olur (19, 20). Yüksek antioksidan içeren besinlerin tüketimi diyet antioksidan kapasitesini artırıcı ve aterojen riskini azaltıcı etkiye sahiptir (17, 19, 21). Bu nedenle antioksidan içeriği yüksek beslenmenin sürdürülmesi önemlidir (Annunziata ve ark., 2021). Fakat literatürde obezite durumu, Plazma Aterojenik İndeks (PAI), Castelli Risk İndeksi (CRI) 1&2, fiziksel aktivite düzeyi ve diyetin antioksidan kapasitesiyle ilişkisini inceleyen çalışma sayısı oldukça sınırlı ve yetersizdir.

Bu çalışma, yetişkin bireylerin aterojenik riskine etki eden faktörlerinin değerlendirilmesi ve diyet antioksidan kapasitesi ile ilişkisinin incelenmesi amacıyla gerçekleştirilmiştir.

2. Gereç ve Yöntem

Çalışma Nisan-Eylül 2023 arasında özel bir tıp merkezinin diyet polikliniğine başvuran hastalar ile yürütülmüştür. G Power 3.1 bilgisayar destekli yazılım programı ile (iki yönlü olarak kurulan hipotez testi ile etki büyüklüğü: 0.2, hata payı: 0.05, araştırmanın gücü: %80) en az 128 katılımcının gerekliliği saptanmış olup, çalışma 143 katılımcı ile tamamlanmıştır (13, 16). Katılımcılar Beden Kütle İndeksi (BKİ) değerine göre obez olan (BKİ≥30 kg/m^2) ve obez olmayan (BKİ<30 kg/m^2) olmak üzere iki gruba ayrılmıştır (22). Çalışmaya başlamadan önce Üsküdar Üniversitesi'nin Girişimsel Olmayan Araştırmalar Etik Kurulu'ndan etik kurul izni ve özel tıp merkezinden kurum izni alınmıştır. Çalışma Helsinki Bildirgesi ilkelerine uygun olarak yürütülmüş ve katılımcılardan çalışmaya başlamadan önce bilgilendirilmiş gönüllü olur formu imzalatılmıştır.

Çalışmanın dışlama kriterleri; "18 yaştan küçük olmak, söylenen ifadeleri kavrama ve uygulama becerisine sahip olmamak (tanısı konulmuş zihinsel veya fiziksel engel durumu vb.), gebe ve emzikli olmak, son 3 aydır herhangi bir besin ögesi takviyesi kullanmak ve kronik böbrek yetmezliği hastası olmak" yer almaktadır. Çalışmanın verileri sosyo-demografik özellikler formu, DASH-Q ölçeği, 24 saatlik besin tüketim kaydı ve Uluslararası Fiziksel Aktivite Formu'nın yer aldığı anket formu ile yüz yüze görüşme yöntemiyle elde edilmiş olup, katılımcıların biyokimyasal verileri araştırma

merkezinin sisteminden hasta onamı ile elde edilmiştir.

Bu çalışmada katılımcıların, diyet kalitelerini belirlemek için Türkçe geçerlik ve güvenirliği Çetin (2020) tarafından yapılmış, DASH-Q Ölçeği kullanılmıştır. Bu ölçekte, düşük yağlı süt ve ürünleri, tam tahıllı ürünler, sebze, meyve, et ve ürünleri, tuz ilave edilmiş besinler ve yağ tüketimlerinin sıklığı değerlendirilmektedir. Bir besin grubu her gün tüketildiyse 7 puan, 6 gün tüketildiyse 6 puan verilmiştir ve bu şekilde tüm ölçek puanlanmıştır. Salamura sebzeler maddesinin puanlanması için ters kodlama işleminin uygulanmıştır. Anket sonucu ≤32 ise diyet kalitesinin düşük olduğunu; 33-51 aralığında ise diyet kalitesinin ortalama olduğunu; ≥52 ise diyet kalitesinin yüksek olduğunu göstermektedir (23).

Katılımcıların fiziksel aktivite düzeylerinin belirlenmesi için Uluslararası Fiziksel Aktivite Anketi (IPAQ) Kısa Formu kullanılmıştır. Son bir hafta içerisinde katılımcıların en az 10 dakika süren şiddetli, orta dereceli ve hafif dereceli fiziksel aktivite süreleri ve sıklığı incelenmiştir (24). Fiziksel aktivite skorunun belirlenmesinde metabolik eşdeğer (MET) değerleri kullanılmıştır. MET değeri ile haftada yapılan yürüyüş ya da aktivitelerin dakikası ve günü çarpılarak bir skor elde edilmiştir. Skor <600 MET-dk/hafta ise fiziksel olarak aktif olmama durumunu, 600-3000 MET-dk/hafta ise fiziksel aktivitenin düşük olma durumunu ve >3000 MET-dk/hafta ise fiziksel olarak yeterince aktif olma durumunu göstermektedir (25).

24 saatlik besin tüketim kaydından elde edilen bilgiler Bilgisayar Destekli Beslenme Programı, Beslenme Bilgi Sistemleri'ne (BeBiS) aktarılmış, ABD Tarım Bakanlığı'nın (USDA) sistemindeki besinlerin ORAC (Oksijen Radikal Absorbans Kapasitesi) değeri referans alınarak bireylerin tükettiği besinlere göre diyetin toplam antioksidan kapasitesi elde edilmiştir (26).

Çalışmanın başında hastaların HDL-K (mg/dL), LDL-K (mg-dL), TG (mg/dL) ve TK (mg/dL) değerleri hekimin ve hastaların bilgisi dahilinde tıp merkezinin laboratuvar sisteminden kaydedilmiştir. Bu veriler kullanılarak logaritma 10 tabanında TG/HDL-K ile PAI değeri hesaplanmıştır. Hesaplanan değer <0.11 olduğunda düşük kardiyovasküler hastalık riski, 0.11-0.24 arasında olduğunda orta kardiyovasküler hastalık riski, >0,24 olduğunda yüksek kardiyovasküler hastalık riski bulunduğu saptanmaktadır (27). Kaydedilen parametrelerden CRI-1 için TK/HDL-K oranı; CRI-2 için LDL-K/HDL-K oranı kullanılmıştır (28). İlgili biyokimyasal parametrelerin oranlanması sonucunda elde edilen CRI-1'in erkeklerde >3.5 ve kadınlarda >3 olması; CRI-2'nin ise her iki cinsiyette de >3.3 olması kardiyovasküler hastalık riskinin bulunduğunu ifade etmektedir (29).

Çalışmadan elde edilen veriler SPSS(Statistical Package for Social Sciences) Statistics for Windows 25.0 programı kullanılarak analiz edilmiştir. Değerlendirilen verilerin ifade edilmesi sayı (n), yüzde (%), ortalama ($\bar{x}$) ve standart sapma (SS) değerleri kullanılmıştır. İstatistiksel analizler için sürekli nicel verilerin dağılım durumlarına göre (parametrik ve nonparametrik) uygun testler kullanılmıştır. Nicel değişkenlerin iki bağımsız grup arasında birbirinden farklılık gösterip göstermediğini test etmek için bağımsız örneklem t testi ve Mann-Whitney U testi uygulanmıştır. İki kategorik değişken arasındaki ilişki ve farklılığı test etmek için ise Kikare testi kullanılmıştır. Sürekli nicel değişkenler arasındaki ilişki ise korelasyon testleri (Pearson /Spearman) ile değerlendirilmiştir. Araştırmada p değerleri 0.05'in altında olan değerler anlamlı kabul edilmiştir.

3. Bulgular

Katılımcılara ait sosyo-demografik özellikler Tablo 1'de verilmiştir. Buna göre, katılımcıların ortalama yaşları 45.14 ±14.59 yıldır. Katılımcıların %76.9 kadın, %62.9 evli, %24.5'i lise mezunu, %29.4'ü özel sektörde çalışmaktadır. Ayrıca katılımcıların, %79.0'u sigara ve %93.0'ü alkol kullanmamaktadır.

Tablo 1. Katılımcıların obezite durumlarına göre sosyo-demografik özellikleri

		Obez (n=71)		**Obez olmayan (n=72)**		**Toplam (n=143)**			
		x̄	**SS**	**x̄**	**SS**	**x̄**	**SS**	**t**	**p**
Yaş (yıl)		47.8	13.73	43.03	15.19	45.14	14.59	1.756	0.081
		n	**%**	**n**	**%**	**n**	**%**	**x^2**	**p**
Cinsiyet	Erkek	16	22.5	17	23.6	33	23.1	0.023	0.999
	Kadın	55	77.5	55	76.4	110	76.9		
Medeni durum	Evli	46	64.8	44	61.1	90	62.9	0.207	0.730
	Bekar	25	35.2	28	38.9	53	37.1		
Eğitim durumu	Okuma yazma biliyor	3	4.2	1	1.4	4	2.8		
	İlkokul	12	16.9	8	11.1	20	14.0		
	Ortaokul	7	9.9	6	8.3	13	9.1	3.284	0.525
	Lise	14	19.7	21	29.2	35	24.5		
	Üniversite/ lisansüstü	35	49.3	36	50	71	49.6		
Çalışma durumu	Kamu çalışanı	5	7.0	7	9.7	12	8.4		
	Serbest meslek	6	8.5	9	12.5	15	10.5	2.172	0.547
	İşsiz	41	57.7	33	45.8	74	51.7		
	Özel sektör	19	26.8	23	32	42	29.4		
Sigara içme	Evet	13	18.3	13	18.1	26	18.2		
	Hayır	57	80.3	56	77.8	113	79.0	0.957	0.725
	Bazen	1	1.4	3	4.1	4	2.8		
Alkol kullanma	Evet	2	2.8	0	0	2	1.4		
	Hayır	63	88.7	70	97.2	133	93.0	4.362	0.086
	Bazen	6	8.5	2	2.8	8	5.6		

**p<0.05; t: Bağımsız örneklem t testi; x^2: Kikare testi*

Katılımcıların diyet kalitesi göstergesi olan DASH-Q değerleri Tablo 2'de verilmiştir. Obez olan katılımcıların % 49.3'ü , obez olmayan katılımcıların %66.7'si düşük diyet kalitesine sahiptir (p< 0.05). Obez olmayan katılımcılarda düşük diyet kalitesi oranı obez olanlara göre istatistiksel olarak anlamlı düzeyde yüksektir (p<0.05).

Tablo 2. Katılımcıların obezite durumuna göre DASH-Q değerleri

	Obez (n=71)		**Obez olmayan (n=72)**		**Toplam (n=143)**			
	n	**%**	**n**	**%**	**n**	**%**	**x^2**	**p**
Düşük diyet kalitesi	35	49.3	48	66.7	83	58.0	4.429	0.043*
Orta-yüksek diyet kalitesi	36	50.7	24	33.3	60	42.0		
	x̄	**SS**	**x̄**	**SS**	**x̄**	**SS**	**t**	**p**
DASH-Q toplam	31.69	10.95	27.68	10.34	29.67	10.8	2.252	0.026*

**p<0.05; t: Bağımsız örneklem t testi; x^2: Kikare testi, DASH-Q: Dietary Approaches to Stop Hypertension-Quality*

Katılımcıların diyet antioksidan kapasitelerinin değerlendirildiği ORAC değeri ortalamaları Tablo 3'te verilmiştir. Buna göre, obez olmayan katılımcıların besin tüketimlerine göre diyet ORAC değerleri, obez olanlara kıyasla daha yüksektir. Ancak, bu durum ancak istatistiksel olarak anlamlı değildir (p>0.05).

Tablo 3. Katılımcıların obezite durumuna göre diyet antioksidan kapasiteleri

	Obez (n=71)			**Obez olmayan (n=72)**			**Toplam (n=143)**				
	x̄	**SS**	**(Q1-Q3)**	**x̄**	**SS**	**(Q1-Q3)**	**x̄**	**SS**	**(Q1-Q3)**	**z**	**p**
ORAC	2740.40	3624.25	(745.30-3527.10)	3676.42	5660.1	(717.53-3853.65)	3211.68	4765.92	(735.00-3609.50)	-0.642	0.521

**p<0.05; z: Mann-Whitney U testi, ORAC: Oksijen Radikal Absorbans Kapasitesi*

Katılımcıların kan lipit düzeyleri ve kardiyovasküler hastalık riskleri Tablo 4'te verilmiştir. Buna göre, çalışmadaki obez katılımcıların obez olmayan katılımcılara kıyasla LDL-K ve TG düzeyleri yüksek (p<0.05) ve HDL-K düzeyleri ise düşüktür (p<0.05). Diğer bir ifadeyle, obez olanların ortalama HDL-K düzeyi 50.70±12.53 mg/dl, obez olmayanlarda ise bu düzey 57.7±18.73 mg/dl'dir. Benzer şekilde obezlerin TG düzeyi 139.16±64.09

mg/dl iken, obez olmayanların ise 116.51±60.12 mg/dl'dir. Aynı şekilde, obezlerin TK düzeyleri obez olmayandan daha yüksek tespit edilmiş olup, bu durum istatistiksel açıdan anlamlı farklılık göstermemektedir (p>0.05). Aterojenik risk açısından değerlendirildiğinde; obezlerin ortalama PAI ve CRI (1&2) risk skorları obez olmayanlardan istatistiksel olarak anlamlı derecede yüksek tespit edilmiştir. Benzer şekilde PAI ve CRI (1&2) risk gruplamasına göre de obez olanlarda olmayanlara kıyasla daha yüksek risk sınıfında bulunma oranı vardır (p<0.05, CRI-2 hariç).

Tablo 4. Katılımcıların obezite durumuna göre kan lipit düzeyleri ve kardiyovasküler hastalık riskleri

	Obez (n=71)			**Obez olmayan (n=72)**			**Toplam (n=143)**				
	x̄	**SS**	**(Q1-Q3)**	**x̄**	**SS**	**(Q1-Q3)**	**x̄**	**SS**	**(Q1-Q3)**	**z/t****	**p**
HDL-K (mg/dl)	50.70	12.53	(41.0-58.0)	57.7	18.73	(46.0-66.0)	54.22	16.28	(44.0-61.4)	-2.650	0.008*
LDL-K (mg/dl)	128.43	35.56	-	116.23	40.94	-	122.29	38.71	-	-2.626**	0.001*
TG (mg/dl)	139.16	64.09	(96.0-166.5)	116.51	60.12	(96.0-166.5)	127.75	62.94	(81.0-154.0)	-2.650	0.013*
TK (mg/dl)	206.15	42.29	-	194.22	43.72	-	200.14	43.28	-	1.657**	0.115
		n	**%**	**n**	**%**		**n**	**%**		**x^2**	**p**
HDL-K (mg/dl)	>40	16	22.5	7	9.7		23	16.1		4.348	0.043*
	<40	55	77.5	65	90.3		120	83.9			
LDL-K (mg/dl)	<130	40	56.3	49	68.1		89	62.2		2.088	0.170
	>130	31	43.7	23	31.9		54	37.8			
TG (mg/dl)	>170	54	76.1	60	83.3		114	79.7		1.171	0.305
	<170	17	23.9	12	16.7		29	20.3			
TK (mg/dl)	>200	35	49.3	42	58.3		77	53.8		1.175	0.316
	<200	36	50.7	30	41.7		66	46.2			
(PAI) Düşük		5	7	25	34.7		30	21			
(PAI) Orta		14	19.8	13	18.1		27	18.9		17.132	<0.001*
(PAI) Yüksek		52	73.2	34	47.2		86	60.1			
		x̄	**SS**	**x̄**	**SS**		**x̄**	**SS**		**t**	**p**
(PAI) Ortalama indeks		0.41	0.24	0.27	0.28		0.34	0.27		3.203	0.002*
		n	**%**	**n**	**%**		**n**	**%**		**x^2**	**p**
(CRI-1) risk yok		9	12.7	27	37.5		36	25.2		11.695	0.001*
(CRI-1) risk var		62	87.3	45	62.5		107	74.8			
		x̄	**SS**	**x̄**	**SS**		**x̄**	**SS**		**t**	**p**
(CRI-1) Ortalama indeks		4.23	1.13	3.61	1.21		3.92	1.21		3.199	0.002*
		n	**%**	**n**	**%**		**n**	**%**		**x^2**	**p**
(CRI-2) risk yok		54	76.1	62	86.1		116	81.1		2.36	0.093
(CRI-2) risk var		17	23.9	10	13.9		27	18.9			
		x̄	**SS**	**x̄**	**SS**		**x̄**	**SS**		**t**	**p**
(CRI-2) Ortalama indeks		2.65	0.91	2.2	0.98		2.42	0.97		2.87	0.005*

**p<0.05; **t: Bağımsız örneklem t testi; z: Mann-Whitney U testi; X^2: Kikare testi; HDL: Yüksek Yoğunluklu Lipoprotein, LDL: Düşük Yoğunluklu Lipoprotein; TG: Trigliserit; TK: Total Kolesteratol; PAI: Plasma Aterojenik İndeks; CRI: Kardiyak Risk İndeks*

Katılımcıların PAI ve CRI (1&2) değerlerinin DASH-Q, ORAC ve IPAQ skorlarıyla korelasyonu Tablo 5'te verilmiştir. Buna göre, obezite durumundan bağımsız olarak çalışma katılımcılarının PAI ve CRI (1&2) değerlerinin DASH-Q, ORAC ve IPAQ ile arasında istatistiksel olarak anlamlı bir ilişki saptanmamıştır (p>0.05).

Tablo 5. Katılımcıların PAI ve CRI (1&2) değerlerinin DASH-Q, ORAC ve IPAQ puanıyla korelasyonu

	PAI		**CRI-1**		**CRI-2**	
	r	**p**	**r**	**p**	**r**	**p**
DASH-Q (toplam)	0.067	0.428	0.095	0.257	0.065	0.438
DASH-Q (obez)	0.127	0.291	0.063	0.602	0.026	0.829
DASH-Q (obez olmayan)	-0.073	0.544	0.037	0.761	0.019	0.872
ORAC (toplam)	-0.016	0.851	-0.059	0.484	-0.079	0.347
ORAC (obez)	-0.008	0.949	-0.133	0.270	-0.137	0.256
ORAC (obez olmayan)	0.008	0.946	0.028	0.815	0.003	0.978
IPAQ puanı (toplam)	0.044	0.606	0.057	0.499	0.033	0.695
IPAQ puanı (obez)	0.215	0.072	0.156	0.194	0.128	0.288
IPAQ puanı (obez olmayan)	-0.091	0.449	0.020	0.870	0.005	0.966

**p<0.05; **p<0.01; Pearson korelasyon, Spearman korelasyon, DASH-Q: Dietary Approaches to Stop Hypertension-Quality ; ORAC: Oksijen Radikal Absorbans Kapasitesi ; IPAQ: Uluslararası Fiziksel Aktivite Anketi*

4. Tartışma

Aterojen oluşumu beslenme, obezite ve fiziksel aktivite gibi faktörlerden etkilenmektedir (14). Bu çalışmada katılımcıların diyet kalitesi olarak DASH-Q skoru, IPAQ puanı, diyet antioksidan kapasitesi göstergesi diyet ORAC değerleri ve aterojen oluşumunu etkileyen risk faktörleri değerlendirilmiştir. Buna göre, aterojen oluşumunun önlenmesi için sağlıklı bir vücut ağırlığında olmanın önemi doğrulanmıştır.

DASH-Q ve obezite durumu arasındaki ilişkiyi incelemeyi amaçlayan araştırmalarda farklı sonuçlar elde edilmektedir. Eskiköy (2024) tarafından yapılan bir araştırmada, obez olmayan katılımcıların genellikle düşük DASH-Q değerine sahip oldukları bulunurken Salari-Moghaddam ve arkadaşları (2022) tarafından yapılan bir araştırmada BKİ değeri arttıkça DASH-Q değerinin azaldığı belirlenmiştir (30, 31). Eskiköy tarafından yapılan araştırmayla paralel olarak bu çalışmada da obez katılımcıların daha yüksek DASH-Q değerine sahip olmasının, obez katılımcıların antioksidandan zengin belirli besinleri daha fazla tüketmelerinden kaynaklandığı düşünülmektedir (31).

Obezite durumu ve diyet antioksidan kapasitesi arasındaki ilişkiyi inceleyen çeşitli araştırmalar farklı sonuçlar ortaya koymaktadır. Çalışkan-Tort (2019)'un kadın katılımcılar ile yaptığı bir araştırmada, obez olan ve olmayan katılımcıların orta seviyede diyet antioksidan kapasitesine sahip olduğu belirlenmiştir (32). Menopoz sonrası kadınlar üzerinde yapılan başka bir çalışmada ise, bu çalışmada olduğu gibi, obez olmayan katılımcıların obez olanlara kıyasla daha yüksek antioksidan kapasitesine sahip olduğu sonucuna ulaşılmıştır (33). Genel olarak literatür incelendiğinde, obez olmayan bireylerin diyet antioksidan kapasitesinin obez ve fazla kilolu bireylere kıyasla daha yüksek olduğu görülmektedir. Bu çalışmada elde edilen bulgular da literatürdeki bulgularla uyum göstermektedir (34).

Doymuş yağ asitleri ve kolesterol açısından zengin bir beslenme, TK, LDL-K ve TG seviyelerinde artışa, HDL-K seviyesinde ise azalmaya neden olmaktadır (35). Kolesterol düzeyleri ile obezite arasındaki ilişkiyi inceleyen araştırmalar, obez katılımcılarda LDL-K, TG ve TK seviyelerinin obez olmayanlara göre daha yüksek, HDL-K seviyesinin ise daha düşük olduğunu göstermektedir (32, 36). Akıcı (2018), obez katılımcılar ile yaptığı çalışmada, referans aralığın altında HDL-K seviyesine sahip olan erkeklerin sayısının kadınlardan fazla olduğu, referans aralığın üzerinde LDL-K seviyesine sahip olan kadınların ise erkeklerden fazla olduğu, ayrıca referans aralığın üzerinde TG seviyesine sahip olan erkeklerin sayısının kadınlardan fazla olduğu belirlenmiştir. Bu bulgular, kolesterol türlerinin cinsiyetlere göre farklı etkileri olduğunu göstermektedir (37). Avşar (2017) yaptığı bir başka araştırmada ise obez katılımcıların yer aldığı grupta, referans aralığın altında HDL-K düzeyine sahip bireylerin grubun %50'sini; referans aralığın üzerinde LDL-K düzeyine sahip bireylerin de yine %50'sini oluşturduğu saptanmıştır (38). Hem bu çalışmada hem de diğer incelenen araştırmalarda, obez katılımcıların yüksek TG ve TK seviyelerinin, yüksek doymuş yağ asidi tüketimine bağlı olabileceği düşünülmektedir (35). Ancak bu çalışmada, referans aralıkta HDL-K ve TG seviyelerine sahip olan obez katılımcıların, obez olmayanlara kıyasla daha fazla olduğu görülmüştür. Bu farklılık, obez katılımcıların mevcut durumda tıbbi beslenme tedavisi alıyor olmaları ve/veya bireysel olarak obezite durumuna yönelik besin tüketimlerine dikkat etme ihtimalinden kaynaklanabileceği düşünülmektedir.

Obezite, aterojenik risk faktörleri arasında önemli bir yer tutmaktadır (39). Kardiyovasküler hastalık risk belirteçlerinden biri olan PAI ile obezite arasındaki ilişkiyi inceleyen araştırmalar, fazla kilolu ve obez katılımcıların PAI değerlerinin normal kilolu katılımcılara göre daha yüksek olduğunu göstermektedir (40, 41). Benzer şekilde, CRI-1 ve obezite arasındaki ilişkiyi inceleyen araştırmalar da PAI ile tutarlı sonuçlar ortaya koymuştur. Anandkumar ve arkadaşlarının (2020) yaptığı bir çalışmada, fazla kilolu ve obez katılımcıların CRI-1 değerlerinin normal kilolu katılımcılara göre daha yüksek olduğu tespit edilmiştir (42). Chong ve arkadaşlarının (2023) yaptığı başka bir çalışmada BKİ ortalaması 29,2 kg/m² olan katılımcıların CRI-1 değerlerinin, BKİ ortalaması 25 kg/m² olan katılımcılardan daha yüksek olduğu belirlenmiştir (43). Hem bu çalışmada hem de diğer araştırmalarda, CRI-1 değerinin BKİ arttıkça yükseldiği görülmüştür. Yüksek BKİ, obezitenin belirlenmesinde; yüksek CRI-1 değeri ise aterojenik risk ve kardiyovasküler hastalık riskinin değerlendirilmesinde önemli bir gösterge olduğundan, obezite ile aterojen oluşumu ve kardiyovasküler hastalık arasında güçlü bir ilişki olduğu düşünülmektedir. CRI-2 ve obezite

arasındaki ilişkiyi inceleyen çalışmalar da benzer bulgular ortaya koymuş, CRI-2 indeksinin BKİ arttıkça yükseldiği görülmüştür (42, 43). Yüksek enerji alımı, basit şekerler ve doymuş yağ asitlerinden zengin bir beslenme tarzı, vücut kütlesinin artmasına ve BKİ'nin yükselmesine neden olarak kardiyovasküler hastalık riskini ve mortaliteyi artırmaktadır (44, 45).

Diyetle alınan antioksidanlar aterosklerotik kardiyovasküler hastalıklardan korunmada etkin rol oynamaktadır (19). Bu bağlamda diyet antioksidan kapasitesi ve aterojenik risk indeksleri arasındaki ilişkiyi incelemeyi amaçlayan ve çoğunlukla fazla kilolu, obez katılımcılar üzerinde yapılan araştırmalarda, bu çalışmadan farklı olarak, plazmanın ferrik indirgeme yeteneği testi kullanılarak hesaplanmış diyet antioksidan kapasitesi ile PAI ve CRI (1&2) arasında istatistiksel olarak anlamlı bir ilişki tespit edilmemiştir (46, 47). Benzer şekilde bu çalışmada da anlamlı ilişki bulunmamıştır. Diyetle alınan antioksidanların aterosklerotik kardiyovasküler hastalıklarına karşı koruyucu olmasına karşın anlamlı bir ilişkinin bulunmama nedeninin, katılımcıların diyet antioksidan kapasitesi yüksek besinler tükettiği kadar kardiyovasküler hastalığa sebep olacak içerikte besinler tüketmesiyle açıklanabilir (48). DASH-Q skoru ile aterojenik risk indeksleri arasındaki ilişkiyi inceleyen çoğunlukla fazla kilolu katılımcılar üzerinde yapılan bir çalışmada DASH-Q skoru ile aterojenik risk indeksleri arasında istatistiksel olarak anlamlı bir ilişki bulunmamıştır (49). Obez katılımcılar üzerinde yapılan bir başka çalışmada, kadınlarda DASH-Q skoruna bağlılığın artmasının PAI değerini değiştirmede etkili olduğu sonucuna varılmıştır (50). Yapılan çalışmalar kardiyorespiratuar kondisyonun PAI değerini azaltabileceğini belirtmektedir (51, 52). Buna bağlı olarak, bu çalışmada dahil olmak üzere literatürdeki çalışmalarda farklı sonuçlar elde edilmesinin katılımcıların fiziksel aktivite düzeyleri olabileceği düşünülmektedir. Fiziksel aktivite ve aterojenik risk indekslerinin incelendiği, çoğunlukla normal kilolu katılımcılar üzerinde yapılan bir çalışmada katılımcıların fiziksel aktiviteleri ile PAI arasında istatistiksel olarak anlamlı bir ilişki bulunmamıştır (53). Fazla kilolu katılımcılar üzerinde yapılan bir başka çalışmada, katılımcıların fiziksel aktiviteleri ile PAI ve CRI (1&2) arasında istatistiksel olarak anlamlı bir ilişki saptanmamıştır (54). Düzenli fiziksel aktivite yapmak ateroskleroz riskini azaltmaktadır. Ancak buna rağmen bu çalışmada fiziksel aktivite ve aterojenik risk indeksleri arasında istatistiksel olarak anlamlı bir ilişki tespit edilmemiştir (55). Bunun nedeni kardiyovasküler hastalığa sebep olan diğer risk faktörleri olabilir.

Bu çalışma, ulusal ve uluslararası literatürde obezite durumu, PAI, CRI (1&2), fiziksel aktivite düzeyi ve diyetin antioksidan kapasitesiyle ilişkisini bütüncül olarak ele alan ilk çalışma olması nedeniyle oldukça önemlidir. Konuyla ilgili ayrı ayrı yapılan çalışmaların sonuçlarında ise farklılıklar ortaya çıkmaktadır. Bu çalışmanın kısıtlılığı örneklem sayısının daha yüksek güven aralığında olmamasıdır. O nedenle örneklem sayısı artırılarak daha fazla araştırma yapılması ve elde edilen sonuçların kanıt düzeyinin bu sayede artırılması erken teşhis ve tedavi için oldukça önemlidir.

5. Sonuç

Bu çalışmada, obezitenin aterojenik riske en fazla etki eden faktör olduğu tespit edilmiştir. Obezite ve aterojenik risk varlığında diyet antioksidan kapasitesi daha düşük olsa da, aralarında istatistiksel olarak anlamlı bir ilişki saptanmamıştır. Aterojen oluşum risklerini azaltmak için bu alanda uzmanlaşmış diyetisyenler ve hekimlerin öncülüğünde diyet antioksidan kapasitesi ve diyet kalitesinin artırılması; fiziksel aktivitenin önemi hakkında toplumun bilinçlendirilmesi, kan lipitlerinin ve kardiyak risk değerlendirilmesi skorlarının düzenli taramalarla incelenmesi ve multidisipliner olarak gerekli tedavilerin uygulanması son derece önemlidir. Böylece, obezite başta olmak üzere morbidite ve mortalitenin en önemli nedenlerinden birisi olan kalp hastalıklarının ortaya çıkışı geciktirilebilir, hatta önlenebilir. Diyet kalitesi ve antioksidan düzeyinin obezite ve kardiyovasküler risk ile olası mekanizma düzeyinde ilişkilerinin aydınlatılması için uzun süreli ve deneysel tasarımda klinik araştırmalara ihtiyaç duyulmaktadır.

KAYNAKLAR

1. World Health Organization Cardiovascular Diseases. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) Erişim 09.03.2024.

2. NHS Cardiovascular disease. https://www.nhs.uk/conditions/cardiovascular-disease/ Erişim 15.01.2024.
3. World Health Organization The Top 10 Causes of Death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death Erişim 22.03.2024.
4. TÜİK https://data.tuik.gov.tr/Bulten/Index?p=Olum-ve-Olum-Nedeni-Istatistikleri-2019-33710 Erişim 22.09.2023.
5. Pala A. Beslenmenin Endotel Disfonksiyonu Üzerine Etkisi. Cerrahi Hastalarda Özel Beslenme ve Diyet Yönetimi. 2020.
6. Yaylalı YT, Küçükaslan M. Endothelial Dysfunction. Pamukkale Tıp Dergisi. 2011;3(152):152-157.
7. Carrascosa C, Francisco R, Francisco S, Raposo A, Saraiva A, Silva H. The cardiovascular therapeutic potential of propolis—A comprehensive review. Biology. 2021;10(1):27.
8. Bergheanu SC, Bodde MC, Jukema JW. Pathophysiology and treatment of atherosclerosis: Current view and future perspective on lipoprotein modification treatment. Netherlands Heart Journal. 2017;25:231-242.
9. Alloza I, Benito-Vicente A, Galicia-García U, Jebari-Benslaiman S, Larrea-Sebal A, Martín C, Rekondo Olaetxea J, Vandenbroeck K. Pathophysiology of atherosclerosis. International Journal of Molecular Sciences. 2022;23(6):3346.
10. Tanaka M. Improving Obesity and Blood Pressure. Hypertension Research. 2020;43(2):79–89.
11. Csige I, Ujvárosy D, Szabó Z, Lőrincz I, Paragh G, Harangi M, et al. The impact of obesity on the cardiovascular system. Journal of diabetes research, 2018;1:3407306.
12. Blair SN, Lavie CJ, Ortega FB. Obesity and cardiovascular disease. Circulation research. 2016;118(11):1752-1770.
13. Ersoy İ, Ersoy P. Yeni Kardiyovasküler Risk Belirteçleri Plazma Aterojenik İndeksi, Nötrofil/Lenfosit Oranı ve Monosit Hdl Oranı Obezitede Nasıl Etkilenmektedir? Kesitsel Retrospektif Bir Çalışma. Kocatepe Tıp Dergisi. 2022;23(1):1-6.
14. Yılmaz HÖ. Akut Koroner Sendrom Tanısı Almış Hipertansif Bireylerde Dash Diyetinin Kardiyak Parametreler Ve Yaşam Kalitesi Üzerine Etkisi. Doktora Tezi. Ankara: Ankara Üniversitesi, Beslenme ve Diyetetik Anabilim Dalı, 2022.
15. Aung M, Bo MS, Cheah WL, Lwin S, Nwe TM, Win TT. Understanding the relationship between atherogenic index of plasma and cardiovascular disease risk factors among staff of an University in Malaysia. Journal of Nutrition and Metabolism. 2018;1:7027624.
16. Kolaç N, Nirgiz C, Balcı AS, Şahinkaya D, Yılmaz E. Ofis çalışanlarında kardiyovasküler hastalık riski ve bilgi düzeyi. Turkish Journal of Cardiovascular Nursing. 2018;9(18):1-6.
17. Atuchin V, Minina V, Ponasenko A, Prosekov A, Vesnina A. Tackling Atherosclerosis via Selected Nutrition. International Journal of Molecular Sciences. 2022;23(15):8233.
18. Değer EB, Vardar SA. Fiziksel Aktivitenin Kısıtlanması: Yetişkin ve Yaşlı Yetişkin Bireyler Arasındaki Farklılıklar. Uludağ Üniversitesi Tıp Fakültesi Dergisi. 2021;47(1):127-132.
19. Annunziata G, Deledda A, Manzin A, Palmas V, Tenore GC, Velluzzi F. Diet-Derived Antioxidants and Their Role in Inflammation, Obesity and Gut Microbiota Modulation. Antioxidants. 2021;10(5):708-730.
20. Im E, Lee Y. Regulation of miRNAs by natural antioxidants in cardiovascular diseases: Focus on SIRT1 and eNOS. Antioxidants. 2021;10(3):377.
21. Calabrese I, Giosuè A, Riccardi G, Vaccaro O. Dietary recommendations for prevention of atherosclerosis. Cardiovascular research. 2022;118(5):1188-1204.
22. World Health Organization A healthy lifestyle. https://www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations Erişim 24.07.2024.
23. Çetin S. DASH Diyet Kalitesi Ölçeği ve Akdeniz Diyetine Bağlılık Öz-Yeterlilik Ölçeğinin Geçerlilik Çalışması. Yüksek Lisans Tezi. İstanbul: Acıbadem Mehmet Ali Aydınlar Üniversitesi, Beslenme ve Diyetetik Anabilim Dalı, 2020.
24. Öztürk M. Üniversitede Eğitim-Öğretim Gören Öğrencilerde Uluslararası Fiziksel Aktivite Anketinin Geçerliliği ve Güvenirliği ve Fiziksel Aktivite Düzeylerinin Belirlenmesi. Yüksek Lisans Tezi. Ankara: Fizik Tedavi ve Rehabilitasyon Programı, 2005.
25. Savcı SÖ, Üniversite öğrencilerinin fiziksel aktivite düzeyleri. Türk Kardiyoloji Derneği Arşivi. 2006;34(3):166-172.
26. Haytowitz, D. B., & Bhagwat, S. (2010). USDA database for the oxygen radical absorbance capacity (ORAC) of selected foods, Release 2. US Department of Agriculture, 3(1), 10-48.
27. Sara V. Tip 2 Diyabetes Mellitus Hastalarında Plazma Aterojenik İndeks ile Mikrovasküler Komplikasyonlar Arasındaki İlişki ve Etki Eden Faktörler. Tıpta Uzmanlık Tezi. İstanbul: Sağlık Bilimleri Üniversitesi, Aile Hekimliği Anabilim Dalı, 2022.
28. Bhardwaj S, Bhatnagar MK, Bhattacharjee J, Tyagi S. Atherogenic Index of Plasma, Castelli Risk Index and Atherogenic Coefficient- New Parameters in Assessing Cardiovascular Risk. International Journal of Pharmacy and Biological Sciences. 2013;3(3):359-364.
29. Olamoyegun MA, Oluyombo R, Asaolu SO, Evaluation of Dyslipidemia, Lipid Ratios, and

Atherogenic Index As Cardiovascular Risk Factors Among Semi-Urban Dwellers in Nigeria. Annals of African Medicine. 2016;15(4):194–199.
30. Eskiköy E. Hipertansiyonu Olan Yetişkin Bireylerde DASH Diyet Kalite Ölçeği ve Beslenme Bilgi Düzeyinin Değerlendirilmesi. Yüksek Lisans Tezi. İstanbul: Atlas Üniversitesi, Beslenme ve Diyetetik Anabilim Dalı, 2024.
31. Salari-Moghaddam A, Nouri-Majd S, Keshteli AH, Emami F, Esmaillzadeh A, Adibi P. Association Between Dietary Total Antioxidant Capacity and Diet Quality in Adults. Frontiers in Nutrition. 2022;9(838752):1-7.
32. Çalışkan Tort F. Obez Olan ve Olmayan Kadınların Diyet Antioksidan Kapasitesi ile Biyokimyasal ve Antropometrik Parametrelerin İlişkilendirilmesi. Yüksek Lisans Tezi. Ankara: Gazi Üniversitesi, Beslenme ve Diyetetik Anabilim Dalı, 2019.
33. Aydogdu N. Diyet Antioksidan Kapasitesi ve Diyet İnflamatuar İndeksinin Menopoz Semptomlarıyla İlişkisi. Yüksek Lisans Tezi. Ankara: Gazi Üniversitesi, Beslenme ve Diyetetik Anabilim Dalı, 2021.
34. Anaya-Morua W, Barajas-Olmos F, Centeno-Cruz F, Contreras-Cubas C, García-Ortiz H, Martínez-Hernández A, et al. Total Antioxidant Capacity in Obese and Non-Obese Subjects and its Association with Anthropo-Metabolic Markers: Systematic Review and Meta-Analysis. Antioxidants. 2023;12(8):1-16.
35. Agarwal R, Khanijau R, Sharma A, Hyperlipidemia: A Review Article. Social Science Review. 2019;5(2):1-12.
36. Keskin N. Obez Adolesanların Beslenme ve Depresyon Durumları Arasındaki İlişkilerin belirlenmesi. Yüksek Lisans Tezi. Ankara: Hacettepe Üniversitesi, Beslenme Bilimleri Programı, 2018.
37. Akıcı G. Hafif Şişman ve Yetişkin Bireylerde Bel-Boy Oranı ile Kardiyovasküler Hastalık Riskinin Belirlenmesi. Yüksek Lisans Tezi. Gaziantep: Hasan Kalyoncu Üniversitesi, Beslenme ve Diyetetik Anabilim Dalı, 2018.
38. Avşar H. Prehipertansif Hastalarda Yaşam Tarzı Değişikliği ve Hipertansiyonu Durdurmaya Yönelik Diyetin (DASH) Etkisinin Belirlenmesi. Doktora Tezi. Ankara: Başkent Üniversitesi, Beslenme ve Diyetetik Anabilim Dalı, 2017.
39. Burke LE, Després JP, Gordob-Larsen P, Lavie CJ, Lear SA, Ndumele CE, et al. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2021;143(21):984–1010.
40. Abbasi B, Javardi MSM, Karandish M, Madani Z, Movahedi A. The Correlation Between Dietary Fat Quality Indices and Lipid Profile with Atherogenic Index of Plasma in Obese and Non-Obese Volunteers: a Cross-Sectional Descriptive Analytic Case-Control Study. Lipids in Health and Disease. 2020;19(213):1-9.
41. Koçak A, Kutlu R, Sayın S. The Relationship Between Atherogenic Index of Plasma and Major Risk Factors of Cardiovascular Disease in Obese and Non-Obese Individuals. The European Research Journal. 2019;5(4):678-685.
42. Anandkumar, Chandrashekhar DM, Jayalakshmi MK, Prashanth B, Impact of Obesity on Castelli's Risk Index I and II, in Young Adult Females. International Journal of Physiology. 2020;8(1):21-26.
43. Chong MY, Huang YC, Hung CF, Lee Y, Lin PY, Tien YT, et al. Comparative Predictive Efficacy of Atherogenic Indices on Metabolic Syndrome in Patients with Schizophrenia. Schizophrenia Research. 2023;262(16):95-101.
44. Martínez JA, Martínez-González MÁ, Navas-Carretero S, Ordovas JM, San-Cristobal R, Contribution of Macronutrients to Obesity: Implications for Precision Nutrition. Nature Reviews Endocrinology. 2020;16(6):305–320.
45. Chooi YC, Ding C, Magkos F, The Epidemiology of Obesity. Metabolism. 2019;92:6-10.
46. Abaj F, Clark CCT, Khosroshahi RA, Koohdani F, Mirzababaei A, Mirzaei K, et al. The Effect of Dietary Total Antioxidant Capacity (DTAC) and Caveolin-1 Gene Variant Interaction on Cardiovascular Risk Factors Among Overweight and Obese Women: A Cross-Sectional Investigation. Clinical Nutrition. 2021;40(8):4893–4903.
47. Chrzczanowicz J, Drygas W, Gawron-Skarbek A, Jeigier A, Kostka J, Kostka T, et al. Cardiovascular Risk Factors and Total Serum Antioxidant Capacity in Healthy Men and in Men with Coronary Heart Disease. BioMed Research International. 2014;2014(özel sayı): 1-8.
48. Chaudhry H, Cottrill CL, Dilip A, Lakhani HV, Pillai SS, Shapiro JI, et al. Therapeutic Efficacy of Antioxidants in Ameliorating Obesity Phenotype and Associated Comorbidities. Frontiers in Pharmacology. 2020;11(1234):1-20.
49. Azadbakht L, Geravand F, Heidari-Seyedmahalle M, Jalalzadeh M, Mahmoodi M, Montazer M, et al. Association Between DASH and Novel Atherogenic Risk Factors, Anthropometric Indices and Foot Ulcer Indicators in Type 2 Diabetic Patients with Foot Ulcer: a Cross-Sectional Study. Journal of Diabetes & Metabolic Disorders. 2024:1-13.
50. Farhangi MA, Jafarabadi MA, Khodarahmi M, Melanocortin-4 Receptor (MC4R) rs17782313 Polymorphism Interacts with Dietary Approach to Stop Hypertension (DASH) and Mediterranean Dietary Score (MDS) to Affect Hypothalamic Hormones and Cardio-Metabolic Risk Factors Among Obese Individuals. Genes & Nutrition. 2020;15(13):1-12.
51. Cristi-Montero C, Ferrari GLDM, Plaza-Díaz J,

Reyes-Ferrada W, Rodríguez-Rodríguez F, Sadarangani KP, et al. Cardiorespiratory Fitness, Physical Activity, Sedentary Time and Its Association with the Atherogenic Index of Plasma in Chilean Adults: Influence of the Waist Circumference to Height Ratio. Nutrients. 2020;12(5):1-11.

52. Blaha MJ, Edwards MK, Loprinzi PD, Influence of Sedentary Behavior, Physical Activity, and Cardiorespiratory Fitness on the Atherogenic Index of Plasma. Journal of Clinical Lipidology. 2017;11(1):119-125.
53. Feng J, Huang Q, Huang Q, Liu Z, Liu Z, Wei M, et al. The atherogenic index of plasma and carotid atherosclerosis in a community population: a population-based cohort study in China. Cardiovascular diabetology. 2023;22(1):125.
54. Barbalho SM, Bechara MD, Quesada K, Tofano R. Castelli Index and estimative of LDL-c particle size may still help in the clinical practice?. Journal of Cardiovascular Disease Research. 2016;7(2):86.
55. Çalıkuşu HR, Tanrıverdi, M, Usluer İN. Kronik hastalıklarda koruyucu rehabilitasyon yaklaşımları ve fiziksel aktivite. Anatolian Clinic the Journal of Medical Sciences. 2023;28(2):225-234.

Osmangazi Journal of Med, 2025;47(1):61-69
DOI: 10.20515/otd.1591896

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Determination of Risk Factors for Allergic and Non-Allergic Rhinitis

Alerjik ve Non-Alerjik Rinit Risk Faktörlerinin Belirlenmesi

[1]Nurhan Kasap, [2]Mustafa Safa Tural, [1]Gizem Uslu, [1]Pınar Yağmur Altınkaynak, [1]Dilek Kacar, [1]Ayşe Cavidan Sonkur, [1]Fatma Bal Çetinkaya, [1]Leman Tuba Karakurt, [1]Özlem Cavkaytar, [1]Mustafa Arga

[1]Department of Paediatric Allergy-Immunology, Istanbul Medeniyet University, Istanbul, Türkiye
[2]Department of Paediatric, Istanbul Medeniyet University, Istanbul, Türkiye

ORCID ID of the authors
NK. 0000-0001-5432-4076
MST. 0000-0002-1539-9355
GU. 0000-0002-4456-2131
PYA. 0000-0002-8297-1315
DK. 0000-0003-4567-321X
ACS. 0000-0001-6910-4340
FB. 0000-0003-4132-5349
LTK. 0000-0003-0818-8063
ÖC. 0000-0002-5747-7032
MA. 0000-0002-0940-7398

Correspondence / Sorumlu yazar:
Nurhan KASAP

Department of Paediatric Allergy-Immunology,
Istanbul Medeniyet University, Istanbul, Türkiye

e-mail: n_aruci@hotmail.com

Ethics Committee Approval: This study was designed and conducted in accordance with the ethical guidelines set forth in the Declaration of Helsinki, and the study protocol was approved by the Istanbul Medeniyet Universty Goztepe Training and Research Hospital interventional Clinical Researches Ethics Committee (Date: 28.08.2023, Decision No:2023/0548.

Informed Consent: This study did not require informed consent.

Authorship Contributions: Mustafa Arga and Nurhan Kasap conceptualized the study. Mustafa Arga designed and supervised the study. Nurhan Kasap, and Mustafa Arga wrote the manuscript. Nurhan Kasap, Mustafa Safa Tural, Leman Tuba Karakurt, Fatma Bal Çetinkaya, Gizem Uslu, Pınar Yağmur Altınkaynak, Dilek Kacar, Ayşe Cavidan Sonkur, Özlem Cavkaytar, and Mustafa Arga cared for the patients, collected data intellectually, and contributed to the manuscript and discussions. All authors read the manuscript and contributed to the revision and discussions.

Copyright Transfer Form: Copyright Transfer Formwas signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Received : 27.11.2024

Accepted : 02.12.2024

Published : 04.12.2024

Abstract: Allergic rhinitis (AR) and non-allergic rhinitis (NAR) are common respiratory conditions affecting pediatric populations. This study aimed to investigate the risk factors and clinical characteristics of AR and NAR in children. A retrospective study was conducted at Goztepe Professor Suleyman Yalcin City Hospital's Pediatric Allergy and Immunology outpatient clinic. Between August 2023 and August 2024, 327 patients under 18 were diagnosed with AR or NAR. Data were collected through computerized questionnaires completed by parents. Patients were classified into AR and NAR groups based on skin prick tests and specific IgE results. Statistical analysis was performed using SPSS version 26.0. Of the 327 patients, 31.5% were diagnosed with NAR and 68.5% with AR. No significant differences were found in age of diagnosis, gender distribution, or symptom onset age between groups. AR patients had more siblings and house residents (p=0.047, p=0.05, respectively). C-section births and indoor smoking were more prevalent in the AR group (p=0.018, p=0.031, respectively). Breastfeeding for over one year was more common in NAR patients (p=0.011). AR patients more frequently experienced symptom exacerbation during school time (p=0.029). Logistic regression analysis revealed that playing outside and paracetamol use before age 1 increased NAR risk (p=0.008, p=0.044, respectively), while eczema and recurrent wheezing after age 1 increased AR risk (p=0.025, p=0.018, respectively). This study identifies distinct risk factors and clinical characteristics for AR and NAR in pediatric patients, providing valuable insights for differential diagnosis and management strategies in clinical practice.
Keywords: Allergic rhinitis, non-allergic rhinitis, risk factors of rhinitis

Özet: Alerjik rinit (AR) ve non-alerjik rinit (NAR), çocukluk çağının en sık görülen kronik solunum yolu hastalıklarındandır. Bu çalışma, çocuklarda AR ve NAR'ın risk faktörlerini ve klinik özelliklerini araştırmayı amaçladı. Göztepe Profesör Süleyman Yalçın Şehir Hastanesi Çocuk Alerji ve İmmünoloji polikliniğinde, retrospektif olarak, Ağustos 2023 ile Ağustos 2024 arasında başvuran 18 yaş altı hastalar analiz edildi ve 327 hastanın rinit tanısı aldığı belirlendi. Veriler, ebeveynler tarafından elde edilen bilgilerle anket aracılığıyla toplandı. Hastalar, deri prik testleri ve spesifik IgE sonuçlarına göre AR ve NAR gruplarına ayrıldı. İstatistiksel analiz, SPSS versiyon 26.0 kullanılarak gerçekleştirildi. 327 hastanın %31,5'i NAR ve %68,5'i AR tanısı aldı. Gruplar arasında tanı yaşı, cinsiyet dağılımı veya semptom başlangıç yaşı açısından anlamlı fark bulunmadı. AR hastalarının daha fazla kardeşi ve evde yaşayan bireyi olduğu saptandı (p=0,047, p=0,05, sırasıyla). AR grubunda sezaryen doğum ve ev içi sigara içimi daha yaygın bulundu (p=0,018, p=0,031, sırasıyla). NAR hastalarında bir yıldan uzun süre emzirme daha yaygındı (p=0,011). AR hastaları okul zamanında daha sık semptom alevlenmesi yaşamıştı (p=0,029). Lojistik regresyon analizi, dışarıda oynamanın ve 1 yaşından önce parasetamol kullanımının NAR riskini artırdığını (p=0,008, p=0,044, sırasıyla), egzema ve 1 yaşından sonra tekrarlayan hırıltılı solunumun ise AR riskini artırdığını gösterdi (p=0,025, p=0,018, sırasıyla). Bu çalışma, pediatrik hastalarda AR ve NAR için farklı risk faktörlerini ve klinik özellikleri tanımladı ve klinik uygulamada ayırıcı tanı ve yönetim stratejileri için değerli bilgiler sundu.
Anahtar Kelimeler: Alerjik rinit, non-alerjik rinit, rinit risk faktörleri

How to cite/ Atıf için: Kasap N, Tural MS, Uslu G, Altınkaynak PY, Kacar D, Sonkur AC, Bal Çetinkaya F, Karakurt LT, Cavkaytar O, Arga M. Determination of Risk Factors for Allergic and Non-Allergic Rhinitis, Osmangazi Journal of Medicine, 2025;47(1):61-69

1. Introduction

Rhinitis represents a significant health concern affecting approximately 10-40% of the pediatric population globally, exerting considerable influence on children's quality of life, sleep patterns, and academic performance (1). This condition imposes a substantial socioeconomic burden through increased healthcare utilization, treatment costs, and loss of school days (2). Rhinitis can be categorized into two primary types: allergic rhinitis (AR) and non-allergic rhinitis (NAR), distinguished by the presence or absence of relevant aeroallergen sensitization. AR is characterized by symptoms such as rhinorrhea, nasal congestion, sneezing, and elevated levels of allergen-specific IgE or a positive skin prick test (SPT). Conversely, NAR is a less well-defined condition, which some studies suggest may be less severe than AR in specific populations (3). NAR encompasses several subtypes, including vasomotor rhinitis and non-allergic rhinitis with eosinophilia syndrome (4). Notably, various non-allergic conditions can mimic AR symptoms, including infections, hormonal imbalances, physical and chemical agents, anatomical anomalies, and certain medications. Unlike AR, there is no specific laboratory test to confirm NAR, making it primarily a diagnosis of exclusion. An immune-mediated response to environmental allergens such as pollen, dust mites, animal dander, and mold characterizes AR. In contrast, NAR is triggered by non-immunological factors like viral infections, environmental irritants, and sometimes hormonal changes, all contributing to inflammation in the nasal mucosa (2, 5). Together, these conditions are a significant cause of pediatric morbidity worldwide, and both conditions are associated with an increased risk of developing comorbid conditions such as asthma and otitis media (6, 7).

The development of AR in children has been linked to various genetic and environmental risk factors. Environmental elements, particularly airborne pollutants, and allergens, are well-documented in their influence on AR. Exposure to traffic-related air pollution, tobacco smoke, and indoor allergens (e.g., dust mites) has significantly correlated with increased AR prevalence and severity in children (8). Additionally, lifestyle changes and dietary factors have gained attention, with recent studies exploring their role in immune modulation and subsequent AR development. Urbanization, for example, has led to a concentration of these environmental pollutants and allergens, directly correlating with higher AR incidences in pediatric populations in urban settings (8, 9).

Genetic factors also play a crucial role in determining susceptibility to AR. A positive family history of atopy, including asthma or eczema, significantly increases a child's likelihood of developing AR (10). Epigenetic studies have also indicated that prenatal and early childhood exposures to pollutants may alter gene expression, particularly those associated with immune responses, which may predispose children to AR (11). Furthermore, climate change has exacerbated pollen levels and altered seasonal patterns, contributing to longer and more intense allergen exposure periods, especially in temperate regions. This environmental shift has been associated with increased rates of AR in children, as evidenced by studies linking pollen seasons and high allergen counts with AR incidence (12).

While sharing some symptomatic characteristics with AR, NAR operates through distinct mechanisms and involves different risk factors. Viral infections, especially those affecting the respiratory tract, are primary triggers of NAR episodes in children. Additionally, exposure to irritants such as chlorine, strong odors, and air pollution can aggravate NAR symptoms, though these factors do not involve IgE-mediated responses, as seen in AR (13). Studies indicate that children with underlying respiratory conditions, such as chronic rhinosinusitis or structural abnormalities like a deviated septum, may be at a higher risk for NAR, as these conditions may create a predisposition for nasal inflammation independent of allergenic sensitization (14).

Given the overlapping symptoms yet differing etiologies of AR and NAR, precise diagnosis is essential to ensure appropriate treatment strategies. AR is typically managed through allergen avoidance, pharmacotherapy (e.g., antihistamines, intranasal corticosteroids), and in some cases, immunotherapy (2, 10). For NAR, symptom relief is generally achieved through decongestants or saline sprays. However, care must be taken to avoid prolonged use of nasal decongestants due to the risk of rebound congestion (13, 14). Furthermore, addressing environmental exposures—both indoors and outdoors—forms a crucial component of both AR and NAR management strategies, underscoring the importance of preventive measures for these prevalent conditions (8).

In conclusion, AR and NAR present significant health challenges for children, driven by a complex interplay of genetic, environmental, and lifestyle factors. Future research should continue to explore these associations, especially as environmental factors evolve with urbanization and climate change, potentially exacerbating the incidence and severity of pediatric rhinitis (12). Comprehensive management and preventive strategies tailored to these risk factors are essential for improving the quality of life in affected pediatric populations.

2. Material and Methods

This study was conducted at the Goztepe Professor Suleyman Yalcin City Hospital Pediatric Allergy and Immunology outpatient clinic, following approval from the Institutional Review Board (IRB) under protocol number 2023/0548. The study adhered to the principles outlined in the Helsinki Declaration, and informed consent was obtained from all participants.

Pediatric patients under 18 years of age, diagnosed with AR or NAR, who visited the clinic between August 1, 2023, and August 1, 2024, were identified through patient records. Researchers completed a computerized questionnaire-based interview of the participant's parents, including data on living conditions, detailed characteristics of symptoms, associated medical conditions, medication use, specific exposures, emergency department visits, and various socioeconomic parameters. According to the allergy skin prick test and specific IgE results, the patients were classified into AR and NAR. 327 patients; among the whole study population, 31.5% had NAR, and 68.5% were diagnosed with AR. AR was defined as a history of rhinitis symptoms concomitant with a positive SPT and specific IgE. NAR was defined by the same set of symptoms but with a negative SPT. Patients with infectious rhinitis diagnosis or anatomical anomalies were excluded from the study.

Statistical evaluation was performed using the Statistical Package for the Social Sciences (SPSS) version 26.0. The normal distribution of continuous variables was inspected through visual and analytical tests. Categorical variables were represented as frequencies (n) and percentages (%), with differential analyses conducted using the chi-square or Fisher's exact test where appropriate. Bonferroni correction was wielded to find the groups with more than two groups. Continuous variables adhering to a normal distribution were expressed via the mean ± standard deviation (SD), and comparative analyses between distinct groups were explored via Student’s t-test. For data non-normal distribution, median values [interquartile range (IQR)] were presented, and the Mann-Whitney U test was used to search for comparative analysis between groups. To investigate the risk factors of NAR and AR, a set of predictor variables, namely age of diagnosis, gender, and other factors, were found to be different between groups due to univariate analysis, and multivariable binary logistic regression models were employed. The outcomes were stated as odds ratios (ORs) with 95% Confidence Intervals (CIs). The Hosmer–Lemeshow goodness-of-fit test evaluated the appropriateness of model fit. All P-values reported were based on bi-directional hypotheses and were evaluated against a predetermined significance threshold of 5%.

3. Results

Our study included 327 patients; among the whole study population, 31.5% of them had NAR, and 68.5% were diagnosed with AR. 17% of AR patients had pollen allergies, 4.9% had mold allergies, 57.6% had house dust-mite allergies, 17% had cat allergies, 11.2% had dog allergies, and 2.7% had cockroach allergies. No statistical differences were found regarding the age of diagnosis and gender distribution between the two groups ($p>0.05$). Median symptom age was 48.0 [96.0] months in NAR and 53.50 [56.0] months in the AR group, and the difference was not significant ($p=0.77$). There was no difference between the two groups according to current ages (64.0 [86.0] months vs 80.0 [72.0] months, respectively, and $p=0.36$). The mother’s ages of the patients were also similar in AR and NAR groups (30.0±5.6 vs 30.1±5.1 years, and $p=0.88$). The number of siblings and house residents was significantly higher in the AR group than in the NAR group ($p=0.047$, $p=0.05$, respectively). The number of older siblings and siblings who were at school age were also similar in both groups (for NAR:0.0 [1.0] and AR:0.0 [1.0], $p=0.26$ and for NAR:1.0 [1.0] and for AR:1.0 [1.0], and $p=0.16$, respectively). No differences were observed between NAR and AR groups regarding birth weight, birth time, birthplace, and the season of birth ($p>0.05$ for all). The birth rate with C/S was significantly higher in the AR group than in the NAR group (74.1% and 61.2%, $p=0.018$). The ratio of smoking indoors was 58.0% in the AR group, whereas 44.7% in the NAR group, the difference being significant ($p=0.031$). Breastfeeding for more than one year was significantly higher in the NAR group than the AR

group (70.9 vs. 54.9%, respectively, and p=0.011). When the parents' family history was inquired, there was no difference in AR, asthma, atopic eczema, food allergy, allergy to dust/pollen, cat/dog allergy, drug allergy, or nasal polyp of the mother. However, the nasal polyp history of the father was significantly higher in the AR group than in the NAR group (15.6% vs 3.9% and p=0.002). Playing outdoors was more common in the NAR group than in the AR group, and the difference was statistically significant (p=0.015). The detailed results are summarized in Table 1.

Table 1. Baseline characteristics of the non-allergic and allergic rhinitis groups

	Non-allergic rhinitis (n=103)	**Allergic rhinitis (n=224)**	**p**
Girl Boy	44 (42.7) 59 (57.3)	102 (45.5) 122 (54.5)	0.63
Age of diagnosis (month)	84.8 ±56.5	85.5±48.4	0.91
Number of residents in the home	4.0 [1.0]	4.0 [2.0]	***0.005***
Siblings	1.0 [2.0]	2.0 [3.0]	***0.047***
Complementary feeding	2.0 [4.0]	2.0 [4.0]	0.48
Age of preschool (years)	3.0 [0.0]	3.0 [0.0]	0.12
Age at start of vitamin D use (months)	1.0 [1.0]	1.0 [2.0]	0.25
Regular use of Vit D	71 (69.6)	172 (77.1)	0.15
Exposure to cigarette smoke during pregnancy	27 (26.2)	47 (21.0)	0.29
Indoor smoking	46 (44.7)	130 (58.0)	***0.031***
Intubation	7 (6.8)	14 (6.3)	0.85
Having a Pet at Birth	9 (8.7)	11 (4.9)	0.18
Prepartum depression	1 (1.0)	11 (4.9)	0.11
Smoking during pregnancy	10 (9.7)	16 (7.1)	0.43
Use of antibiotics in the first week of birth	3 (2.9)	15 (6.7)	0.20
Use of antibiotics in the first month of birth	10 (9.7)	23 (10.3)	0.88
Breastfeeding None <6 months 6-12 months > 1 year*	 - 16 (15.5) 14 (13.6) 73 (70.9)	 7 (3.1) 36 (16.1) 58 (25.9) 123 (54.9)	***0.011***
Playing outdoor less than once/week more than twice/week	 32 (31.1) 71 (68.9)	 101 (45.3) 122 (54.7)	***0.015***

The variables were presented as number (%), mean ± SD, or median [IQR]
**The group in which the difference was aroused according to Bonferroni correction.*

Table 2 shows the patients' symptoms. The symptoms of admission, severity, and the symptoms' beginning were similar in the NAR and AR groups. However, the increment of the symptoms during school time was more common in the AR group than the NAR group (68.8% vs 56.3%, p=0.029). There were no differences in conjunctivitis symptoms between the two groups (p>0.05 for all), as well as sinusitis and asthma symptoms (p>0.05).

Table 2. The features of the symptoms of the patients with non-allergic and allergic rhinitis

Symptoms	**Non-allergic rhinitis (n=103)**	**Allergic rhinitis (n=224)**	**p**
Rhinorrhea	77 (74.8)	156 (69.6)	0.34
Nasal Itching	62 (60.2)	136 (60.7)	0.93
Sneezing	56 (54.4)	122 (54.5)	0.99
Snoring	20 (19.4)	60 (26.8)	0.15
Postnasal Discharge	46 (44.7)	115 (51.3)	0.26
Anosmia	5 (4.9)	7 (3.1)	0.43
Open mouth sleeping	44 (42.7)	77 (34.4)	0.15
The severity of the symptoms	7.0 [2.0]	6.0 [1.0]	0.34
Persistent Intermittent	68 (67.3) 33 (32.7)	167 (75.6) 54 (24.4)	0.12
Severity Mild Moderate/Severe	 44 (42.7) 59 (57.3)	 118 (57.9) 105 (47.1)	 0.087
Beginning of preschool/school	31 (30.1)	88 (39.3)	0.11
Increment in school	58 (56.3)	154 (68.8)	***0.029***
Symptoms of Conjunctivitis			
Tearing/Discharge	39 (37.9)	71 (31.7)	0.27
Itching	29 (28.2)	54 (24.1)	0.44
Redness	36 (35.0)	59 (26.3)	0.11
Congestion	8 (7.8)	14 (6.3)	0.61
Symptoms of Sinusitis			
Rhinorrhea/Postnasal Discharge	41 (39.8)	67 (30.0)	0.082
Throat cleaning	7 (6.8)	16 (7.1)	0.91
Hyposmia/anosmia	1 (1.0)	4 (1.8)	1.0
Headache	11 (10.7)	33 (14.7)	0.32
Tonsillectomy	5 (4.9)	20 (8.9)	0.20
Recovery of symptoms post-tonsillectomy	3 (2.9)	16 (7.1)	0.20
Recurrent Symptoms	1 (1.0)	2 (0.9)	1.0
Ventilation tube	-	7 (68.5)	-
Nasal polyps	1 (1.0)	2 (0.9)	1.0
Obstructive sleep apnea syndrome	-	5 (2.2)	-
Asthma	8 (7.8)	20 (8.9)	0.73
Symptoms of Asthma			
Cough	10 (9.7)	16 (7.1)	0.43
Dyspnea	7 (6.8)	9 (4.0)	0.28
Wheezing	9 (8.7)	16 (7.1)	0.62

The variables were presented as number (%), mean ± SD, or median [IQR]

Risk factors for NAR and AR are shown in Table 3 according to exposure age (<1 year and >1 year). In those below 1 year of age, paracetamol use was significantly more common in the NAR group than in the AR group (94.1% vs 86.1%, p=0.035). Furthermore, traffic/factory smoke exposure was significantly higher in the AR group than in the NAR group (p=0.013) in patients aged 1 year and younger. On the other hand, it was seen that at age 1 year older, eczema was more common in the AR group than the NAR group (p=0.024). Patients with AR more commonly had wheezing more than three times per week compared to patients with NAR (27.2% vs 15.5% and p=0.021).

Table 3. Risk factors for non-allergic and allergic rhinitis according to age

	Non-allergic rhinitis (n=103)	**Allergic rhinitis (n=224)**	**p**
< 1 year of age			
Antibiotics usage 0 1 2	 32 (31.1) 59 (57.3) 12 (11.7)	 98 (43.9) 107 (48.0) 18 (8.1)	0.078
Paracetamol usage	96 (94.1)	192 (86.1)	***0.035***
Ibuprofen usage	75 (75.0)	152 (81.3)	0.21
Cat at home	2 (1.9)	4 (1.8)	1.0
Dog at home	3 (2.9)	6 (2.7)	1.0
Eczema	3 (2.9)	19 (8.5)	0.093
Food allergy	2 (1.9)	8 (3.6)	0.73
Recurrent Wheezing	15 (14.6)	30 (13.4)	0.86
Middle ear infection	8 (7.8)	16 (7.2)	0.86
Living at Home with Wood-Coal Heating	10 (9.7)	14 (6.3)	0.26
Exposure to Traffic /Factory smoke	9 (8.7)	44 (19.6)	***0.013***
Living in a rural area	4 (3.9)	6 (2.7)	0.51
Exposure to cigarette smoke	40 (38.8)	96 (42.9)	0.49
Formula, 6 months	32 (31.1)	70 (31.4)	0.95
Formula	17 (16.5)	47 (21.0)	0.34
Hospitalization due to LRTI	12 (11.7)	25 (11.2)	0.90
>1 year of age			
Antibiotics usage	102 (99.0)	220 (98.2)	0.58
Paracetamol usage	102 (99.0)	224 (100.0)	-
Ibuprofen usage	99 (96.1)	211 (94.2)	0.47
Cat at home	9 (8.7)	29 (12.9)	0.27
Dog at home	9 (8.7)	21 (9.4)	0.85
Eczema	4 (3.9)	27 (12.1)	***0.024***
Food allergy	2 (1.9)	8 (3.6)	0.73
Wheezing	16 (15.5)	61 (27.2)	***0.021***
Middle ear infection	30 (29.1)	56 (25.0)	0.43
Living at Home with Wood-Coal Heating	8 (7.8)	11 (4.9)	0.30
Exposure to Traffic /Factory smoke	14 (13.6)	28 (12.6)	0.80
Living in a rural area	3 (2.9)	5 (2.2)	0.71
Exposure to cigarette smoke	40 (38.8)	111 (49.6)	0.071
Hospitalization due to LRTI	9 (8.7)	25 (11.2)	0.51

The risk factors for AR and NAR were investigated by binary logistic regression analysis (backward method). After adjustment for age, gender, and other variables found in univariate analysis, playing outside with friends and using paracetamol for under 1 year increased the risk of NAR. Furthermore, eczema and frequent wheezing after 1 year of age increased the risk of AR. The detailed results are seen in Table 4.

Table 4. Multivariable logistic regression analysis of the possible risk factors NAR and AR

	Odds Ratio	**95 % Confidence Interval**	**p**
Non-allergic Rhinitis			
Playing outdoors less than once/a week	2.04	1.20-3.45	0.008
Use of paracetamol before 1 year old	2.63	1.02-6.67	0.044
Allergic Rhinitis			
Eczema after 1 year	3.55	1.17-10.76	0.025
Wheezing after 1 year	2.15	1.14-4.05	0.018

Variables were adjusted for age of diagnosis, sex, increment of the symptoms in school, playing outdoors, use of paracetamol before 1 year old, eczema after 1 year old, wheezing after 1 year old, and exposure to traffic or factory smoke before 1 year old of age.

4. Discussion and Conclusion

This study reveals several underlying patterns and associations that warrant careful consideration, particularly in the pediatric population, by comprehensively analyzing risk factors for allergic rhinitis AR and NAR. The investigation encompassed 327 patients, with 31.5% diagnosed with NAR and 68.5% with AR, providing robust data for analysis aligning with current epidemiological patterns (2, 5). A striking finding was the significant correlation between indoor smoking exposure and AR; AR patients demonstrated significantly higher indoor smoking exposure compared to the NAR group. Additionally, our results indicated that traffic and factory smoke exposure was significantly associated with AR development in children under one year of age.

Our study demonstrates a significant association between paternal history of nasal polyps and AR. Furthermore, our analysis indicated that breastfeeding duration beyond one year had significant protective effects against AR development. Multivariate analysis identified several critical, independent risk factors: limited outdoor activity increased the risk of NAR, while eczema and recurrent wheezing after one year of age increased the risk of AR. Early life exposures proved particularly important in our findings, with paracetamol use being more common in the NAR group before one year of age. We observed that traffic and factory smoke exposure in the first year of life had a stronger association with AR development. School attendance emerged as a significant factor in our study, with AR patients showing more pronounced symptom exacerbation during school periods. Notably, we found that the number of siblings and house residents was significantly higher in the AR group compared to the NAR group.

The environmental exposure analysis in the study revealed convincing correlations, with traffic and factory smoke exposure in the first year of life being more strongly associated with the development of AR compared to the NAR group (19.6% vs. 8.7%). Parmes et al. (7) showed that traffic-related air pollution and factory smoke exposure significantly affect the development of AR in children under one year of age. Recent epidemiological studies have shown that the prevalence of AR varies significantly by geographic region and level of urbanization. Wu et al. (8) showed that urban environmental factors are becoming increasingly important, with studies showing that higher concentrations of environmental pollutants are directly associated with the increased incidence of AR in metropolitan areas. Environmental pollutants play an increasingly important role in the exacerbation of symptoms. The effects of climate change have become increasingly important, and studies show changing pollen patterns and extended exposure times. This environmental change has contributed to the changing AR and NAR presentation patterns in pediatric populations (13, 14).

The study revealed an interesting connection between paternal nasal polyp history and AR, with a 15.6% prevalence in AR patients compared to 3.9% in NAR patients. This finding underscores the potential genetic component in AR development. Studies have demonstrated that children with a family history of atopy have a significantly higher risk of developing AR (11). Recent epigenetic studies have further illuminated how immune mediators and genetic and environmental factors influence AR development, particularly in immune response modulation (15, 16).

This study's association between early-life paracetamol exposure and NAR aligns with emerging evidence suggesting early medication use may influence immune system development. This finding corroborates research by Beasley et al. (17), who reported a link between paracetamol use in infancy and increased risk of asthma symptoms in childhood. The higher prevalence of paracetamol use in the NAR group before age one than in the allergic rhinitis group warrants further investigation into the potential mechanisms underlying this association. While our results do not establish causality, they underscore the importance of considering early-life exposures in the etiology of NAR. Future longitudinal studies are needed to elucidate the long-term effects of early paracetamol use on respiratory health and to inform evidence-based guidelines for infant medication use.

This analysis yielded compelling evidence regarding the protective effects of extended breastfeeding. This protective effect was markedly more prevalent in the NAR group, with 70.9% of NAR patients having been breastfed for over a year, compared to only 54.9% in the AR group. This finding aligns with and further substantiates the research conducted by Kanchanapoomi et al. (5), who previously reported on the potential immunological benefits of

prolonged breastfeeding in reducing the risk of allergic conditions.

Furthermore, our study revealed that school attendance emerged as a significant factor in the manifestation and exacerbation of rhinitis symptoms, particularly for AR patients. We observed a distinct pattern where AR patients exhibited more pronounced symptom exacerbation during school periods compared to non-school periods. This observation is consistent with the findings reported by Goniotakis et al. (2), who documented similar trends in their research. The exacerbation of symptoms during school hours could be attributed to various factors, including exposure to allergens in the school environment, stress associated with academic activities, or changes in daily routines. This finding underscores the importance of considering the educational environment in managing AR in pediatric patients. It suggests the need for targeted interventions to mitigate symptom exacerbation during school hours.

The multivariable analysis conducted in our study unveiled several critical and independent risk factors for both NAR and AR in the pediatric population. A key finding was the association between limited outdoor activity and an increased risk of NAR. This relationship suggests that reduced exposure to outdoor environments may play a role in developing NAR symptoms. The mechanism behind this association could be linked to decreased exposure to diverse environmental stimuli or reduced physical activity, which may influence the development and function of the nasal mucosa. Conversely, our analysis revealed that the presence of eczema and recurrent wheezing after one year of age were significant risk factors for the development of AR. The association between eczema and AR is particularly noteworthy, as it aligns with the 'atopic march' concept. This finding corroborates the observations made by Yum et al. (14), who documented complex interrelationships between various allergic conditions. The link between eczema and AR suggests a shared underlying immunological dysfunction that may predispose individuals to multiple allergic manifestations. These findings are consistent with comprehensive reviews of pediatric rhinitis risk factors (8, 9, 18, 19). Such alignment with existing literature lends credibility to our results and underscores their relevance within the broader context of pediatric rhinitis research.

Treatment implications suggest the need for differentiated approaches to AR and NAR management. The distinct risk profiles identified for each condition necessitate tailored therapeutic strategies, particularly considering the role of environmental modifications (20). Future interventions should focus on modifiable risk factors, especially in urban settings with high pollution exposure. The significant association between indoor smoking and AR emphasizes the importance of smoke-free environments and regular ventilation of indoor spaces in prevention strategies.

The study's strengths lie in its comprehensive assessment of risk factors across different age groups and environmental contexts. However, future research should focus on longitudinal outcomes and intervention effectiveness to better inform clinical practice and public health policies. Our study has limitations, including geographical limitations and lack of time frame assessments.

Our findings contribute significantly to understanding risk factors for both AR and NAR in pediatric populations. These provide valuable insights for developing targeted preventive strategies for both AR and NAR in pediatric populations. The results emphasize the importance of early intervention, environmental modification, personalized treatment approaches, and regular follow-up protocols based on specific risk profiles. Continued research is essential, particularly regarding the long-term impacts of early-life exposures and the effectiveness of preventive strategies in different environmental contexts.

REFERENCES

1. Sih T, Mion O. Allergic rhinitis in the child and associated comorbidities. Pediatr Allergy Immunol. 2010;21(1 Pt 2):e107-13.
2. Goniotakis I, Perikleous E, Fouzas S, Steiropoulos P, Paraskakis E. A Clinical Approach of Allergic Rhinitis in Children. Children (Basel). 2023;10(9).
3. Settipane RA, Schwindt C. Chapter 15: Allergic rhinitis. Am J Rhinol Allergy. 2013;27(3):52-5.
4. Kaliner MA. The treatment of vasomotor non-allergic rhinitis. Clin Allergy Immunol. 2007;19:351-62.
5. Kanchanapoomi K, Srisuwatchari W, Pacharn P, Visitsunthorn N, Jirapongsananuruk O. The natural

history of childhood-onset non-allergic rhinitis; a long-term follow-up study. Asian Pac J Allergy Immunol. 2023.
6. Licari A, Magri P, De Silvestri A, Giannetti A, Indolfi C, Mori F, et al. Epidemiology of Allergic Rhinitis in Children: A Systematic Review and Meta-Analysis. J Allergy Clin Immunol Pract. 2023;11(8):2547-56.
7. Parmes E, Pesce G, Sabel CE, Baldacci S, Bono R, Brescianini S, et al. Influence of residential land cover on childhood allergic and respiratory symptoms and diseases: Evidence from 9 European cohorts. Environ Res. 2020;183:108953.
8. Wu AC, Dahlin A, Wang AL. The Role of Environmental Risk Factors on the Development of Childhood Allergic Rhinitis. Children (Basel). 2021;8(8).
9. Ferrante G, Asta F, Cilluffo G, De Sario M, Michelozzi P, La Grutta S. The effect of residential urban greenness on allergic respiratory diseases in youth: A narrative review. World Allergy Organ J. 2020;13(1):100096.
10. Fireman P. Therapeutic approaches to allergic rhinitis: treating the child. J Allergy Clin Immunol. 2000;105(6 Pt 2):S616-21.
11. Morin A, McKennan CG, Pedersen CT, Stokholm J, Chawes BL, Malby Schoos AM, et al. Epigenetic landscape links upper airway microbiota in infancy with allergic rhinitis at 6 years of age. J Allergy Clin Immunol. 2020;146(6):1358-66.
12. Eguiluz-Gracia I, Mathioudakis AG, Bartel S, Vijverberg SJH, Fuertes E, Comberiati P, et al. The need for clean air: The way air pollution and climate change affect allergic rhinitis and asthma. Allergy. 2020;75(9):2170-84.
13. Poddighe D, Gelardi M, Licari A, Del Giudice MM, Marseglia GL. Non-allergic rhinitis in children: Epidemiological aspects, pathological features, diagnostic methodology and clinical management. World J Methodol. 2016;6(4):200-13.
14. Yum HY, Ha EK, Shin YH, Han MY. Prevalence, comorbidities, diagnosis, and treatment of non-allergic rhinitis: real-world comparison with allergic rhinitis. Clin Exp Pediatr. 2021;64(8):373-83.
15. Albloushi S, Al-Ahmad M. Exploring the latest understanding on the role of immune mediators, genetic and environmental factors in pathogenesis of allergic rhinitis: a systematic review. Front Allergy. 2023;4:1223427.
16. Martin MJ, Garcia-Sanchez A, Estravis M, Gil-Melcon M, Isidoro-Garcia M, Sanz C, et al. Genetics and Epigenetics of Nasal Polyposis: A Systematic Review. J Investig Allergol Clin Immunol. 2021;31(3):196-211.
17. Beasley RW, Clayton TO, Crane J, Lai CK, Montefort SR, Mutius E, et al. Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents: International Study of Asthma and Allergies in Childhood Phase Three. Am J Respir Crit Care Med. 2011;183(2):171-8.
18. Tran MM, Lefebvre DL, Dharma C, Dai D, Lou WYW, Subbarao P, et al. Predicting the atopic march: Results from the Canadian Healthy Infant Longitudinal Development Study. J Allergy Clin Immunol. 2018;141(2):601-7 e8.
19. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: Many trajectories, many pathways. J Allergy Clin Immunol. 2019;143(1):46-55.
20. Zhu X, Zhang Q, Du X, Jiang Y, Niu Y, Wei Y, et al. Respiratory Effects of Traffic-Related Air Pollution: A Randomized, Crossover Analysis of Lung Function, Airway Metabolome, and Biomarkers of Airway Injury. Environ Health Perspect. 2023;131(5):57002.

Osmangazi Journal of Med, 2025;47(1):70- 84
DOI: 10.20515/otd.1551048

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Ruh Sağlığı Profesyonellerinin Paylaşılan Travmatik Gerçeklik ve Baş Etme Deneyimleri: Nitel Bir Çalışma

Shared Traumatic Reality and Coping Experiences of Mental Health Professionals: A Qualitative Study

[1]Şeyma Sehlikoğlu [2]Esra Bekircan

[1]Adıyaman Üniversitesi, Tıp Fakültesi, Psikiyatri Anabilim Dalı, Adıyaman, Türkiye
[2]Trabzon Üniversitesi Tonya Meslek Yüksek Okulu, Tıbbi Hizmetler ve Teknikler Bölümü, Trabzon, Türkiye

ORCID ID of the authors

ŞS. 0000-0002-9512-713X
EB. 0000-0001-5942-026X

Correspondence / Sorumlu yazar:
Şeyma SEHLİKOĞLU

Adıyaman Üniversitesi, Tıp Fakültesi, Psikiyatri Anabilim Dalı, Adıyaman, Türkiye

e-mail: seymashlk@gmail.com

Abstract: The experiences of mental health professionals exposed to social trauma is an under-researched topic. The aim of this study is to examine the shared traumatic reality and coping experiences of mental health professionals exposed to social trauma. Using an inductive qualitative approach, this study was conducted through in-depth interviews with 18 mental health professionals who directly experienced the earthquake in Turkey on February 6, 2023 and provided mental health services in the earthquake zone. The data obtained from the interview were collected under 5 categories and 16 subcategories. Since the participants experienced shared traumatic reality, identification, double exposure and traumatic countertransference against social trauma, they stated that they experienced feelings such as helplessness, sadness, inadequacy and guilt more intensely, and exhibited hyperarousal and avoidance behaviors against trauma. The participants reported that they struggled to meet their basic needs in the disaster area and that their workload increased due to both the inadequacy of physical infrastructure and the high number of trauma patients visiting the clinic. They stated that they tried to cope with the traumatic process they experienced by using social support systems and that they turned to drug use to reduce the destructive effects of trauma. They stated that they became stronger by learning after their traumatic experiences and experienced posttraumatic growth. Supporting mental health professionals in developing effective coping strategies and resilience in the face of societal traumas can have a protective impact on both their mental well-being and their professional competence.
Keywords: Collective Trauma, Shared Traumatic Reality, Earthquake, Mental Health Professionals.

Özet: Toplumsal travmaya maruz kalan ruh sağlığı profesyonellerinin deneyimleri yeterince araştırılmamış bir konudur. Bu çalışmanın amacı toplumsal travmaya maruz kalmış ruh sağlığı profesyonellerinin paylaşılan travmatik gerçeklik ve baş etme deneyimlerini incelemektir. Bu çalışma tümevarımsal nitel yaklaşım kullanılarak Türkiye'de 6 Şubat 2023 tarihinde gerçekleşen depremi doğrudan yaşayan ve deprem bölgesinde ruh sağlığı hizmeti veren 18 ruh sağlığı profesyoneli ile derinlemesine görüşme yolu ile gerçekleştirilmiştir. Görüşmeden elde edilen veriler 5 kategori ve 16 alt kategori altında toplanmıştır. Katılımcılar toplumsal travmaya karşı paylaşılan travmatik gerçeklik, özdeşim, çifte maruziyet ve travmatik karşı aktarım yaşadıklarından bahsetmişlerdir. Travmaya karşı çaresizlik, üzüntü, yetersizlik ve suçluluk gibi duyguları daha yoğun yaşadıklarını, aşırı uyarılma ve kaçınma davranışı sergilediklerini ifade etmişlerdir. Katılımcılar afet bölgesinde temel ihtiyaçlarını karşılama noktasında zorlandıklarını ve gerek fiziksel alt yapı yetersizliği gerek çok fazla travma hastasının kliniğe başvurması sonucunda iş yüklerinin arttığını bildirmişlerdir. Yaşadıkları travmatik süreç ile sosyal destek sistemlerini kullanarak baş etmeye çalıştıklarını ve travmanın yıkıcı etkilerini azaltmak için ilaç kullanımına yöneldiklerini belirtmişlerdir. Yaşadıkları travma deneyimlerinden sonra öğrenerek güçlendiklerini ve travma sonrası büyüme yaşadıklarını belirtmişlerdir. Ruh sağlığı profesyonellerinin toplumsal travmalar karşısında olumsuz etkilenmemesi adına etkin baş etme ve güçlenme noktasında desteklenmeleri ruh sağlıkları ve mesleki profesyonellikleri üzerinde koruyucu etki yapabilir.
Anahtar Kelimeler: Toplumsal Travma, Paylaşılan Travmatik Gerçeklik, Deprem, Ruh Sağlığı Profesyonelleri.

Etik Kurul Onayı: Çalışma Trabzon Üniversitesi Sosyal ve Beşeri Bilimler Bilimsel Araştırma ve Yayın Etik Kurulu tarafından onaylanmıştır. Karar no: 2023-10/2.3 Tarih: 20.10.2023
Telif Hakkı Devir Formu: Tüm yazarlar tarafından Telif Hakkı Devir Formu imzalanmıştır.
Yazar Katkısı: Veri toplama: ŞS, EB. Konsept: ŞS, EB. Tasarım: ŞS, EB. Veri İşleme: EB. Analiz veya Yorum: ŞS, EB. Literatür Taraması: ŞS, EB. Yazma: ŞS, EB.
Çıkar Çatışması Beyanı: Yazarlar arasında herhangi bir çıkar çatışması bulunmamaktadır.
Destek ve Teşekkür Beyanı: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received : 16.09.2024
Accepted :.06.12.2024
Published :.16.12.2024

How to cite/ Atıf için: Sehlikoğlu Ş,Bekircan E, Ruh Sağlığı Profesyonellerinin Paylaşılan Travmatik Gerçeklik ve Baş Etme Deneyimleri: Nitel Bir Çalışma, Osmangazi Journal of Medicine, 2025;47(1):70-84

1. Giriş

İnsanlık tarihi boyunca bireyler travmatik olaylar ve felaketlerle yüzleşmek zorunda kalmıştır (1). Toplumsal travmatik olaylar "kişinin düzen, öngörülebilirlik, güvenlik ve kimlik hakkındaki normal varsayımlarını geçersiz kılan bir deneyim, başa çıkma kaynaklarının azami düzeyde enerjilendirilmesini gerektiren çok ciddi bir çevresel zorluk" olarak tanımlanmıştır (2). Toplumsal travmatik olaylar bireyleri ve toplumu sosyoekonomik, psikososyal, sosyodemografik ve politik yönleri ile çok boyutlu olarak etkilemektedir (3,4). Bu etkiler bireyler üzerinde sağ kalım suçluluğu, fiziksel ve psikosomatik yakınmalarda artış, uyku bozuklukları, mizaç değişiklikleri, şüphecilik, hafıza sorunları, faillerin düşüncelerini içselleştirme ve suçluluk, ebeveynlik rollerinde yetersizlik, yakın ilişki kurma güçlükleri, madde kötüye kullanımı gibi birçok belirti ve sendroma yol açabilmektedir (5).

Travmaya uğrayan bireylerle temas halinde olan ruh sağlığı profesyonellerinde rahatsız edici imgeler, hatırlatıcılar ve ipuçlarından kaçınma, aşırı uyarılma, olumsuz duygular ve işlevsellikte bozulma gibi birincil travma ile benzer semptomlar görülebilmektedir (6). Travmatik olaylara karşı gelişen duygusal ve davranışsal tepkiler bilişsel yaklaşımla incelendiğinde, bireylerin olayları nasıl algıladıkları ve yorumladıklarının bu tepkiler üzerinde belirleyici olduğu görülmektedir (7). Travmatik yaşantılar sonucunda bireyler, korkular, kabuslar, yoğun duygusal tepkiler, disosiyatif reaksiyonlar ve somatizasyon gibi çeşitli psikolojik belirtiler geliştirebilir (8). Travmatize olmuş bireylerle çalışan ruh sağlığı profesyonelleri hastalara travmalarını veya travma sonrası stres bozukluğunu yönetmelerine yardımcı olmaya çalışırlarken ikincil travmatik stres yaşayabilmektedirler (9). İkincil travmatik stres, bireyin ciddi biçimde strese yol açan bir duruma ya da trajik bir olaya tanık olması, bu olaya ilişkin bilgiye sahip olması ya da işi nedeniyle dolaylı olarak travmaya maruz kalması sonucunda yaşadığı duygudurum ve stres tepkisidir (10). İkincil travmatik stres ruh sağlığı profesyonellerinin travma mağdurlarının anlatılarından nasıl etkilendiklerini anlamalarına yardımcı olsa da mağdurlar ile aynı travmatik ortamı paylaştığındaki deneyimlerini kapsamlı bir şekilde açıklayamamaktadır (11). Ruh sağlığı profesyonellerinin travma mağdurları ile aynı olay veya olaylara maruz kaldığı durumlar "paylaşılan travmatik gerçeklik" olarak adlandırılmaktadır (12, 13). Paylaşılan travmatik gerçeklik, travma mağdurunun ve ruh sağlığı profesyonelinin tecavüz, çocuk istismarı gibi aynı bireysel travmaya maruz kalmasıyla olabileceği gibi, aynı etnik gruba, aynı topluluğa ait olmalarından kaynaklanan toplumsal travmalara maruz kalmalarıyla da oluşabilir (12). Psikodinamik yaklaşıma göre bireyler travmatik deneyimlerle yüzleşirken bilinçdışı süreçler travmatik gerçekliğin nasıl algılandığını belirler. Paylaşılan travmatik gerçeklik kavramı, ruh sağlığı profesyonellerinde duygusal ve fiziksel tükenmişlik hissini ve mesleki yeterlilik algısını olumsuz yönde etkilese de aynı zamanda terapötik empatiyi derinleştirerek mesleki bağlılığı artırma, kişisel gelişim ve dayanıklılık sağlama gibi olumlu katkılar sunabilir (14).

Paylaşılan travmatik gerçeklik kavramı ruh sağlığı profesyonellerinin kişisel/aile yaşamı ile iş yaşamı arasında belirsiz sınırlara yol açabilmektedir. Paylaşılan travmatik gerçeklik varoluşsal tehditlere yol açarak iş hayatı ile özel hayat arasındaki sınırları bulanıklaştırır (15). Travmatize olmuş kişiler ile çalışırken aynı maruz kalma ve yeterlilik seviyelerine rağmen bazı ruh sağlığı profesyonelleri hastaların travmatik öykülerinden daha fazla etkilenirken bazıları ise etkilenmemektedir (16). Bu etkilenme boyutlarının farklı olmasında baş etme mekanizmalarının etkinliği ön plana çıkmaktadır (17). Travma sonrası stres ile baş etmede sosyokültürel etkilerin, biyopsikososyal kuramsal çerçeveler bağlamında anlaşılması gerektiği vurgulanmaktadır. Biyopsikososyal model, stres tepkisini şekillendiren içsel başa çıkma stratejileriyle birlikte sosyal destek ve ilişkisel dinamikler gibi dışsal kaynakları da içeren kişiler arası başa çıkma mekanizmalarını kapsamlı bir bütünlük içinde değerlendirir (18). Sosyal destek, sağlık ve iyilik halinin temel bir unsuru olarak, travmaya maruz kalan bireyler ve bu alanda çalışan profesyonellerin yaşadıkları içsel çatışma ve stresi yönetmelerine yardımcı olurken, travma sonrası iyileşme süreçlerini hızlandırmakta ve bu sürecin daha etkili bir şekilde tamamlanmasını sağlamaktadır (19). Travma sonrası birey, yeni duruma adapte olabilmek için travmatik olayın öğretilerini de içine alan esnek, gerçekçi bilişsel çıkarımlar kazanır. Travma sonrası büyüme özellikle bilişsel süreçler yoluyla gelişmekte ve bireylerin yaşamları hakkında yeni anlamlar geliştirmesine olanak tanımaktadır (20).

Depremler son yıllarda yaşanan toplumsal travmalardan biridir (21). Yakın zamanda 6 Şubat 2023 tarihinde Türkiye'de Doğu Anadolu Fayı üzerinde meydana gelen depremler sonucu Hatay, Kahramanmaraş, Adıyaman, Malatya, Gaziantep,

Elazığ, Osmaniye, Şanlıurfa, Diyarbakır, Kilis ve Adana olmak üzere toplam 11 ilde önemli miktarda hasar ve yıkım meydana gelmiştir (22). 11 ilde binlerce binanın yıkılmasına, on binlerce insanın ölmesine sebep olan bu büyük afet deprem bölgesindeki hastanelerin yıkılmasına ve zarar görmesine yol açarak (23) afet bölgesinde çalışan insanların temel ihtiyaçlarını karşılama ve sağlık hizmetlerini sağlama noktasında zorlanmalarına yol açmıştır. Ayrıca deprem bölgesinde yaşayan sağlık çalışanları da birer travma mağduru oldukları için hem nitelikli eleman eksikliği hem de sağlık hizmetleri alt yapısının zarar görmesi nedeniyle afetin yarattığı sonuçlar daha ciddi boyutlara ulaşmıştır (24, 25).

Deprem bölgesinde travma sonrası stres bozukluğu ve birçok ruhsal bozukluk bakımından risk altında bulunan ruh sağlığı profesyonelleri hastaları ile aynı travmaları yaşadıkları ve onların travmalarına tanıklık ettikleri için paylaşılan travma bakımından hassas gruptadırlar (11). Afet bölgesinde hem travma mağduru olan hem de yardım edici konumunda bulunan ruh sağlığı profesyonellerinin paylaşılan travmatik gerçeklik ve başa çıkma süreçlerinde deneyimlerinin belirlenmesi ilerleyen dönemlerde ihtiyaçların karşılanması ve stres yönetimi açısından önemli sonuçlar doğurabilir. Ruhsal travma ile çalışan ve kendisi de aynı ruhsal travmayı yaşamış olan ruh sağlığı profesyonellerinin yaşadıkları zorluğu açıklayan çalışmalara ihtiyaç olduğu düşünülmüştür. Bu çalışmanın temel amacı afetlerde görev almış ve ayrıca o afeti yaşamış olan ruh sağlığı profesyonellerinin paylaşılan travmatik gerçeklik ve baş etme deneyimlerini belirlemektir. Bu bağlamda bu çalışmadan elde edilecek sonuçlar ile toplumsal travmaların ruh sağlığı profesyonelleri üzerindeki etkisinin belirlenmesi bakımından alan yazına katkı sağlayacağı düşünülmektedir

2. Gereç ve Yöntem

2. 1. Araştırmanın Amacı ve Deseni

Bu çalışmanın amacı toplumsal travmaya maruz kalmış ruh sağlığı profesyonellerinin paylaşılan travmatik gerçeklik ve baş etme deneyimlerini incelemektir. Bu çalışma tümevarımsal nitel araştırma türünde yapılmıştır. Nitel araştırmanın amacı, bireylerin yaşadıkları olayları nasıl anlamlandırdıklarına dair bir bakış açısı oluşturmak ve bu süreci genel hatlarıyla açıklayarak, bireylerin deneyimlerini nasıl değerlendirdiklerini incelemektir (26).

2. 2. Araştırmanın Yeri ve Zamanı

Araştırma Nisan-Temmuz 2024 tarihleri arasında depremin etkilediği illerden biri olan Adıyaman ilinde yapılmıştır.

3. 3. Araştırmanın Evren ve Örneklemi

Araştırmanın evrenini deprem travmasını doğrudan yaşamış olan ve deprem bölgesinde görev yapan ruh sağlığı profesyonelleri oluşturmuştur. Araştırmanın örneklemini ise deprem bölgelerinden biri olan Adıyaman ilinde bulunan üçüncü basamak bir hastanede çalışan veya Adıyaman'da gönüllü ruh sağlığı hizmeti veren ruh sağlığı profesyonelleri oluşturmuştur. Bu çalışmada örneklem grubunda yer alan ruh sağlığı profesyonellerinin içerisinde psikiyatrist, psikiyatri hemşiresi ve psikologlar yer almaktadır. Örneklem seçiminde amaçlı örneklem yöntemi kullanılmıştır. Amaçlı örnekleme yönteminde, sınırlı kaynakların en etkin şekilde kullanımı için çalışılan konuda bilgili ve deneyimli olan kişilerin/grupların belirlenmesi ve seçimi söz konusudur (27).

Çalışmaya dahil edilme kriterlerinde 6 Şubat 2023 Türkiye depremini doğrudan yaşamış olmak, bu bölgede depremzedelere psikolojik destek vermiş olmak ve araştırmaya gönüllü olarak katılım şartı aranmıştır. Depremi yaşamamış olanlar, deprem sonrası ruh sağlığı hizmeti vermemiş olanlar ve çalışmaya dahil olmak istemeyenler çalışma dışında bırakılmıştır. Buna bağlı olarak dahil olma ölçütlerini karşılayan ve amaçlı örnekleme yöntemi ile ulaşılan 18 ruh sağlığı profesyoneli çalışma grubunu oluşturmuştur. Fenomenolojik araştırmalarda örneklem büyüklüğüne ilişkin farklı görüşler olmakla birlikte genel olarak çalışmalar için 10-15 kişinin yeterli olduğu değerlendirilmektedir (28). Niteliksel araştırmalarda doygunluğa önem verilmektedir ve bu kapsamda herhangi bir farklı veri elde edilmeyene kadar araştırmanın devam ettirilmesi söz konusudur (27). Katılımcı sayısının belirlenmesinde verilerin doygunluğa ulaşması esas alınmıştır ve çalışmada veri doygunluğuna 18 katılımcı ile ulaşılmıştır. Her bir katılımcı ile yapılan görüşmelerden sonra görüşme kayıtları incelenmiş ve 18. katılımcı ile beraber artık farklı bir kategori ve alt kategorinin elde edilmediği anlaşılınca görüşme 18. kişi ile beraber sonlandırılmıştır. Katılımcıların kimlik bilgilerinin gizliliğinin sağlanabilmesi için her bir katılımcıya K1, K2… şeklinde kodlar verilmiştir. Çalışmaya dahil olan ruh sağlığı profesyonellerinin demografik bilgilerinin dağılımı Tablo 1'de görülmektedir.

Tablo 1. Afetlerde görev almış ruh sağlığı profesyonellerine ilişkin demografik veriler

Katılımcı	Yaş	Cinsiyet	Meslek	Depremden sonra psikiyatrik tanı alma	Mesleki deneyim süresi (yıl)	Daha önce herhangi bir afette görev alma deneyimi
K1	36	Erkek	Psikolog	Anksiyete bozukluğu	8	Hayır
K2	35	Kadın	Psikiyatrist	Hayır	3	Hayır
K3	36	Erkek	Psikiyatri Hemşiresi	Depresyon	8	Hayır
K4	27	Kadın	Psikiyatrist	Hayır	1	Hayır
K5	31	Kadın	Psikiyatrist	Depresyon, TSSB	1	Hayır
K6	31	Kadın	Psikiyatrist	TSSB	4,5	Hayır
K7	28	Kadın	Psikiyatrist	Hayır	3	Hayır
K8	27	Kadın	Psikiyatrist	Panik bozukluk	3	Hayır
K9	29	Kadın	Psikiyatrist	Panik bozukluk	5	Hayır
K10	37	Erkek	Psikiyatrist	Hayır	10	Hayır
K11	37	Erkek	Psikiyatrist	TSSB	8	Hayır
K12	34	Erkek	Psikiyatrist	Hayır	10	Hayır
K13	47	Kadın	Psikiyatrist	Hayır	25	Hayır
K14	33	Erkek	Psikiyatrist	TSSB	7	Evet
K15	47	Erkek	Psikolog	Hayır	24	Evet
K16	42	Erkek	Psikolog	Hayır	12	Hayır
K17	30	Kadın	Psikiyatri Hemşiresi	Hayır	5	Hayır
K18	43	Kadın	Psikiyatrist	TSSB	10	Hayır

Tablo 1 incelendiğinde katılımcıların büyük çoğunluğunun psikiyatrist olduğu, yarısından fazlasının kadın, yaş aralığının 27 ile 47 arasında değiştiği ve tamamına yakınının daha öncesinde herhangi bir afette görev almadıkları görülmektedir. Çalışmada yer alan ruh sağlığı profesyonellerinin bazılarının depremden sonra anksiyete bozukluğu, depresyon, panik bozukluk ve TSSB tanılarını aldıkları görülmektedir.

2. 4. Veri Toplama Aracı ve Veri Toplama Süreci

Araştırmacılar tarafından hazırlanan anket soruları içerisinde demografik bölüm ve yarı yapılandırılmış görüşme formu bulunmaktadır. Demografik bilgi formunda katılımcıların yaş, cinsiyet, meslek, mesleki deneyim süresi, afet deneyimleri ve deprem sonrası psikiyatri tanısı almalarına ilişkin sorular bulunmaktadır. Yarı yapılandırılmış görüşme formunda afetlerde görev almış ruh sağlığı profesyonellerinin paylaşılan travmatik gerçeklik ve baş etme deneyimlerini keşfetmeye yönelik açık uçlu sorular bulunmaktadır. Araştırmacılar, 'Cevabınızı biraz daha açıklayabilir misiniz?' ve 'Bununla ne demek istiyorsunuz?' gibi sonda soruları kullanılmıştır. Bu çalışmanın verileri 12 katılımcıyla yüz yüze gerçekleştirilen bireysel derinlemesine görüşmeler yoluyla toplanmış, ulaşım zorlukları ve yoğun çalışma koşulları nedeniyle 6 katılımcı ile online görüşmeler yapılmıştır. Oluşturulan yapılandırılmış sorular ile ilgili nitel araştırma ve travma alanlarında deneyimli üç farklı uzmandan görüş alınmıştır. Görüşler doğrultusunda form gözden geçirilmiş ve forma son hali verilmiştir (Tablo 2).

Tablo 2. Afetlerde görev almış ruh sağlığı profesyonellerinin paylaşılan travmatik gerçeklik ve baş etme deneyimlerine yönelik soru formunda yer alan açık uçlu sorular

Sorular	
1.	Kişisel ve profesyonel hayatınızın depremden nasıl etkilendiğini açıklar mısınız?
2.	Travma mağdurları ile görüşme yaparken hissettiklerinizden bahseder misiniz
3.	Travma mağdurları ile aynı travmayı yaşamak sizin için ne anlama geliyor?
4.	Kendiniz de birer travma mağduru iken travma hastalarına ruh sağlığı hizmeti verirken neler yaşadığınızı anlatır mısınız?
5.	Deprem travması yaşamış bireylere ruh sağlığı hizmeti verirken hangi duyguları hissettiniz açıklar mısınız?
6.	Travma hastaları ile çalışırken ve deprem bölgesinde yaşarken yaşadığınız olumsuzluklar ile nasıl başa çıktınız?

2.5. Araştırma Süreci

Çalışmanın verilerini oluşturan görüşmelere başlamadan önce ana katılımcılar dışında üç katılımcı ile pilot görüşmeler yapılmıştır. Sözü edilen pilot görüşmeler doğrultusunda, görüşme sürecinde ve sorularında gerekli görülen revizyonlar yapıldıktan sonra bu pilot görüşmeler çalışma dışı bırakılmıştır. Nitel veri toplama sürecinde katılımcılara çalışmanın amacı, çalışmanın ne kadar süreceği, katılımcıların araştırmacıya ulaşması için isim ve iletişim bilgileri paylaşılmıştır. Yapılan çalışmanın katılımcıların payına düşen olası yararları ve onlara bir karşılık sağlayıp sağlamayacağı izah edilmiştir. Araştırmanın parçası olarak, çalışmada bir bilgilendirilmiş onam formu kullanılmıştır. Onam formu aracılığıyla katılımcılardan araştırmaya katılımlarına ve ses kaydına onay verdiklerine dair izin alınmıştır. Yüz yüze yapılan görüşmeler ses kayıt cihazı aracılığı ile diğer görüşmeler ise online yapılmıştır ve araştırmacı haricinde başka kimsenin ulaşamayacağı bir bilgisayara aktarılarak şifreli şekilde saklanmıştır. Katılımcılar ile görüşmeler 40–60 dakika arası sürmüştür.

2.6. Araştırmanın Etik Yönü

Araştırmanın yapılabilmesi için Trabzon Üniversitesi Sosyal ve Beşerî Bilimler Bilimsel Araştırma ve Yayın Etiği Kurulu'ndan 2023-10/2.3 sayılı (20.10.2023 tarihli) etik kurul onayı alınmıştır. Araştırmada Adıyaman Eğitim ve Araştırma Hastanesi'nde çalışan katılımcılar için yazılı kurum izni alınmıştır. Adıyaman ilinde depremi yaşayan ve bu bölgede depremden sonra gönüllü ruh sağlığı hizmeti veren ruh sağlığı profesyonellerinden ise yazılı ve sözlü onam alınmıştır. Araştırmanın tüm aşamalarında Helsinki Deklarasyonuna uygun hareket edilmiş olup katılımcılardan yazılı ve sözlü bilgilendirilmiş onam alınmıştır. Katılımcılarımızın ve araştırma ekibimizin refahı bu çalışma boyunca en büyük öneme sahip olmuştur. Herhangi bir katılımcı önemli bir sıkıntı bildirirse psikolojik destek kaynaklarına yönlendirilmiştir.

2.7. Verilerin analizi

Bu çalışmada eleştirel gerçekçi veriler elde etmek için Braun ve Clarke tarafından belirtilen tematik analiz yöntemi kullanılmıştır (29, 30). Tematik analize uygun olarak tüm transkriptleri okuyup tekrar okuyarak görüşmeler üzerinde düşünerek ve araştırma ekibi toplantılarında ortaya çıkan kategorileri tartışarak veriler keşfedilmeye çalışılmıştır. Bu süreçte kategori ve alt kategorileri saklama, analiz etme, raporlama ve görselleştirmeye yardımcı olması için nitel veri analizi yazılım programı olan MAXQDA-24 kullanılmıştır (31). Veri setinde sıklıkla tekrarlanmış, katılımcılar tarafından yoğun vurgu yapılmış olay ve olgulara yönelik veriler belli kavramlar yani kategoriler ve alt kategoriler çerçevesinde bir araya getirilir ve yorumlanır (32).

Tüm ifadelerin transkript edilmesiyle kategoriler ve alt kategoriler elde edilmiştir. Elde edilen bu kategori ve alt kategorilerin güvenirliğini sağlamak için araştırmada elde edilen ifadeler birbiri ile etkileşimi olmayan ve araştırmada yer almayan 2 farklı uzman ile paylaşılarak onlardan destek alınmıştır.

2.8. Analiz Stratejisi

Araştırmanın toplumsal travma temelinde yürütülmesi nedeniyle Kretsch (33) ve Saakvitne (34) tarafından belirtilen paylaşılan travmatik gerçeklik kavramı bu çalışmaya yön vermiştir. Kretsch dinamik psikoterapi alanında çalışan profesyonellerin hastaları ile aynı krize maruz kaldıklarında neler hissettiklerine ve bunun hastaları ile aralarındaki profesyonel ilişkiye yansımaları sonucu paylaşılan travmatik gerçeklik kavramına atıf yapmıştır. Ruh sağlığı profesyonellerinin bireyin iç

dünyasına odaklanırken kültürün, dilin ve yaşadıkları toplumda meydana gelen olayların etkisinden muaf olmadıklarını belirtmiştir (33). Bu çalışmada paylaşılan travmatik gerçeklik kavramından yola çıkılarak aynı deprem travmasını yaşamış ruh sağlığı profesyonellerinin hastalarına ruh sağlığı hizmeti verirken travmadan etkilendikleri öngörülmüştür.

Bu araştırmada hem dinamik hem de bilişsel yaklaşımları harmanlayan hibrit bir metodoloji benimsenmiştir, bu sayede çok yönlü bir analiz sunulmuştur. Bu çalışmaya konu olan paylaşılan travmatik gerçeklik kavramını incelemek için ruh sağlığı profesyonellerinin kavrama ilişkin görüşlerine odaklanılmış olup tümevarımsal bir yaklaşım ile kategori ve alt kategoriler elde edilmiştir. Tümevarımsal tematik analiz yöntemi sistematik ve esnek bir yaklaşımdır (35). Analizlerden elde edilen temalar arasında yer alan paylaşılan travmatik gerçeklik kavramı psikodinamik yaklaşıma dayanırken, travmaya verilen tepkiler ve travma sonrası büyüme kavramları bilişsel kuram çerçevesinde ele alınmıştır. Afet bölgelerinde yaşanan zorluklar ve travma ile başa çıkma süreçleri ise psikososyal bir perspektifle değerlendirilen kavramlardır.

2.9. Araştırma ekibi ve Refleksivite

Refleksivite, tüm nitel araştırmaların önemli bir bileşenidir ve okuyucunun, onu üreten araştırma ekibini daha iyi anlayarak analizin geçerliliğini değerlendirmesini sağlar (36). Katılımcılar ile araştırmacıların ruh sağlığı profesyonellerinden oluşmaları ve katılımcılar ile araştırmacıların travma alanında deneyimlerinin olması katılımcıların görüşlerini daha rahat ifade etmelerini sağlamış olabilir. Böylelikle araştırmacıların depreme ilişkin hem deneyimlerinin olması hem de travma hastalarına ruh sağlığı hizmeti vermiş olmalarından dolayı refleksivitenin veri toplama ve çalışma sürecine olan etkileri belirtilmiş olmuştur.

2.10. Kalite ve geçerlilik

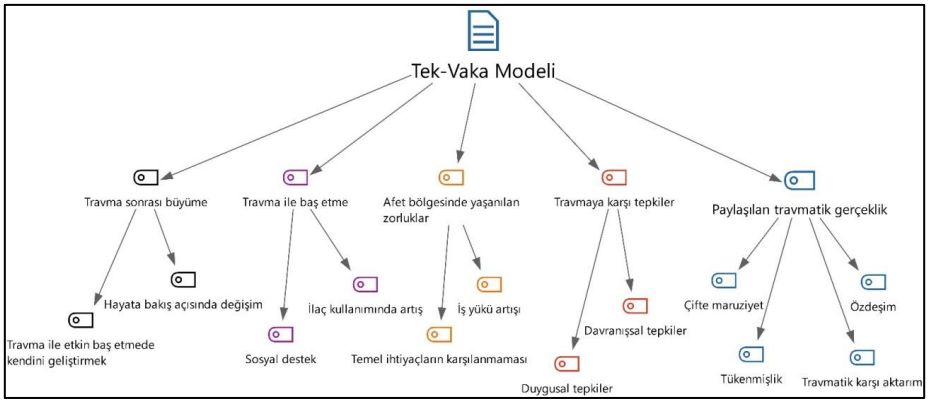
Bu çalışma boyunca Niteliksel Araştırmaları Raporlama Standartları (Consolidated Criteri a for Reporting Qualitative Research (COREQ)) (37) takip edilmiştir. Nitel araştırmalarda geçerlilik, aktarılabilirlik ve itibara dikkat edilmiştir (38). Sonuçların geçerliliğini arttırmak için, veri toplama, kodlama ve analiz süreçlerine araştırmada yer alan araştırmacılar dışında 2 farklı araştırmacı dahil edilmiştir. Uzman görüşüne başvurulan araştırmacılardan bireysel olarak veri toplama araçları ve verilerin analizine ilişkin uzman görüşleri alınmıştır. Uzman görüşüne başvurulan kişilerin deprem deneyimlerinin olmasına dikkat edilmiştir. Alınan uzman görüşler doğrultusunda araştırmacılar kendi varsayımlarını, yanlılıklarını sorgulayarak ortaya çıkan gözlemleri tartışmak için araştırma süreci boyunca düzenli olarak toplantılar yapmışlardır. Yorumların güvenilirliğini artırmak için, çalışmayı yürüten araştırma ekibi ve bu verileri inceleyen dış araştırmacıların şeffaf olmalarına dikkat edilmiştir. Yapılan bu çalışmada geçerliliği desteklemek amacıyla; katılımcıların ayrıntılı bilgilerinin alınmasına, katılımcıların çalışmaya dahil edilme ve dışlama kriterlerinin belirlenmesine, görüşmeler esnasında katılımcıların sunmuş olduğu ifadelerin özetlenmesine ve bunların doğruluğuna ilişkin katılımcı geri dönütleri alınmasına özen gösterilerek veri üçgenlemesinin (39) yapılmasına dikkat edilmiştir.

3. Bulgular

Yapılan tematik analizi sonrası 5 kategori ve 16 alt kategori belirlenmiştir. Buna göre, paylaşılan travmatik gerçeklik, travmaya karşı tepkiler, afet bölgesinde yaşanılan zorluklar, baş etme mekanizmaları ve travma sonrası büyüme şeklinde beş kategori elde edilmiştir (Tablo 3, Şekil 1).

Tablo 3. Kategori ve alt kategorilere ilişkin bulgular

Kategoriler	Alt Kategoriler
Paylaşılan travmatik gerçeklik	Travmatik karşı aktarım Özdeşim Tükenmişlik Çifte maruziyet
Travmaya karşı tepkiler	Duygusal tepkiler: Çaresizlik, Üzüntü, Yetersizlik, Suçluluk Davranışsal tepkiler: Aşırı uyarılma, Kaçınma
Afet bölgesinde yaşanılan zorluklar	Temel ihtiyaçların karşılanamaması İş yükü artması
Travma ile baş etme	Sosyal destek İlaç kullanımında artış
Travma sonrası büyüme	Travma ile etkin baş etmede kendini geliştirmek Hayata bakış açısında değişim



Şekil 1. Kategori ve Alt Kategorilere İlişkin Tek Vaka Modeli

3.1. Paylaşılan travmatik gerçeklik

Bu çalışmada belirlenen ilk kategori katılımcıların travmaya ortak maruz kalmalarının bir sonucu olarak paylaşılan travmatik gerçeklik olmuştur. Paylaşılan travmatik gerçeklik karşısında travmatik karşı aktarım yaşadıklarından, hastaları ile yoğun özdeşim kurduklarından, travmaya doğrudan ve dolaylı maruz kaldıkları için çifte maruziyetlerinin olduğundan ve tükenmişlik yaşadıklarından bahsetmişlerdir. Bu kategoriyi oluşturan alt kategorilere ilişkin katılımcı görüşlerinden örnekler aşağıda gösterilmektedir:

Travmatik karşı aktarım: Katılımcılar depremi doğrudan deneyimledikleri ve hastaların deprem deneyimlerine meslekleri gereği dolaylı olarak da maruz kaldıkları için çifte maruziyet yaşadıklarını ve hastaların deneyimlemiş olduğu travmalara karşı bir aktarım yaşadıklarını belirtmişlerdir. Travmatik karşı aktarım kategorisine yönelik katılımcı ifadelerine örnekler:

"Kendim de depremzede olduğum ve deprem sırasında ve sonrasında tüm zorlukları yaşayan bir psikiyatrist olarak depremin hemen sonrasında hastaları dinleyip onlara yardımcı olmaya çalışmak hem çok zor hem de yıpratıcıydı. Hastanın anlattıklarını o an ben de tekrar yaşadığımı hissettim" (K8)

"Kendim de bir depremzede olduğum için maalesef insanlar travmalarını anlatırken onların hikayelerinde kendimden her defasında bir şeyler buluyorum." (K12)

"Benzer travmaları yaşadığım için her muayene sonrası travmalarım nüksetti." (K15)

Özdeşim: Katılımcılar yaşadıkları travma sonrasında hastaları gibi maddi ve manevi kayıplar ve benzer acılar yaşadıkları için hastalar ile yoğun özdeşim kurduklarını ifade etmişlerdir. Bu kategoriye yönelik katılımcı ifadelerine örnekler:

"Hasta depremde çocuğunu ve eşini kaybettiğinden bahsediyor. Ya ben de kaybetseydim, enkaz altında kalsaydım düşünceleri aklıma geliyor. Sürekli ağlama isteği var. Bazen hastalar anlatınca ağlayasım geliyor." (K8)

"Kendim de depremi yaşayıp aile üyelerimden kaybettiklerim olduğu için hastaların yaşadığı zorlukları dinlerken yaşamış olduğum tüm süreç gözümün önüne geliyordu." (K6)

"En yakın arkadaşımı kaybettim, evimiz ağır hasarlıydı yakın zamanda yıkıldı. Yine de diğer insanlara hizmet vermeye çalışıyoruz. Onların anlattığı herşeyi çok iyi anlıyorum. Gerçekten ruhsal desteğe ihtiyaçları var" (K18)

"Onlara bakarken fazla empati yapmak zorunda kaldım. Çünkü ben de aslında bir hastaydım, mağdurdum." (K10)

Tükenmişlik: Katılımcılar hastalar ile aynı travmayı hem yaşadıklarını hem de tekrarlı olarak hastaların travmalarını dinledikleri için tükenmişlik yaşadıklarını belirtmiştir. Tükenmişlik kategorisine yönelik katılımcı ifadelerinden bazı örnekler:

"Yaşadığım travmadan ve zorlu çalışma şartlarından sonra çoğunlukla artık hiçbir şey yapmaya motivasyonum kalmadı. İnsanlarla iletişimim zaruriyet dışında hiç yok denecek düzeyde." (K5)

"Depremi bizzat 8 yıldır yaşadığım bölgede çalışmak birçok yakınlık kurduğum ve uzun takipli hastalarımı kaybetmek ve kendi tanıdığım insanların da ölmesi beni çok kötü etkiledi. Tükendiğimi hissediyorum." (K11)

Çifte maruziyet: Katılımcılar hastalara ruh sağlığı hizmeti verirken onların travmalarına tekrar tekrar maruz kaldıklarından dolayı travmaya karşı çifte maruziyet yaşadıklarını belirtmişlerdir. Ayrıca deprem bölgesinde hem yaşayıp hem de çalışmaya devam etme sonucunda travmaya maruziyetlerinin daha da arttığını aktarmışlardır. Çifte maruziyet alt kategorisini aşağıdaki sözlerle ifade etmişlerdir.

"İlk dönemler çok fazla hayat hikayesine şahit olduğum için bir süre tepkisiz kaldığımı, şaşkınlık üzüntü gibi duygularımın normal süreçten faklı işlediğini süreç ilerledikçe fark etmeye başladım. Bir süre geçtikten sonra özellikle tanıdığım insanların ve bazen de bilmediğim tanışmadığım insanların yaşam hikayelerinin zaman zaman aklıma geldiğini bu durumun çalıştığım zamanlarda da zihnimde yer aldığını, bazı durumlarda işimi yapmamda olumsuzluk yarattığını tecrübe ettim." (K3)

"Hem o süreci yaşamak hem de yaşadığın olaylara benzerliğinden dolayı hastaların anlattıkları yoğun bir travma etkisi yaratıyor." (K16)

3.2. Travmaya karşı tepkiler

Katılımcılar hastaneye çok fazla travma hastasının başvurduğundan ve hastaların hayat hikayelerine çok fazla maruz kaldıklarından bahsetmişlerdir. Hastaların travmatik öykülerinin kendi travma deneyimleri ile benzer yanları karşısında travmaya karşı duygusal ve davranışsal tepkilerden bahsetmişlerdir. Bu kategorilere ilişkin alt kategoriler ve katılımcıların görüşlerine ilişkin örnekler aşağıda belirtilmiştir.

Duygusal tepkiler: Bu alt kategori altında katılımcılar yaşadıkları kendi travma deneyimleri ve hastalarının travma deneyimleri karşısında çaresizlik, üzüntü, yetersizlik ve suçluluk duygularını yoğun bir şekilde hissettiklerinden bahsetmişlerdir.

Çaresizlik

Katılımcılar deprem travmasını yaşadıkları için hastalara ruh sağlığı hizmeti verirken yaşadıkları travmanın olumsuz etkileri ve hastalarının mağdur durumları karşısında kendilerini çaresiz hissettiklerini ifade etmişlerdir.

"Hepimiz çok kötü şeyler yaşadık. Hastalara ne yapsam iyi gelir diye düşünüyorum ama hayatta güvensizlik ve çaresizlik duygularını hissettim" (K9)

"Çok yıkıcı ve yıpratıcı. Süreç insanın kendini çok çaresiz ve aciz hissetmesini sağlıyor." (K12)

"TSSB tanısı aldım, depresif duygudurumu, suçluluk, kaçınma, aşırı uyarılma, çaresizlik gibi hislerim vardı." (K5)

Üzüntü

Katılımcıların yaşadıkları travma sonrası hastaları ile yaptıkları görüşmeler sırasında ve sonrasında daha fazla üzüntü yaşadıklarından bahsetmişlerdir.

"Çok fazla üzüntü, kaygı, endişe, göğüs ağrısı, nefes darlığı yaşadım." (K7)

"Depremzede olup deprem bölgesinde çalışmak zorunda olmak ruhsal açıdan çok zorlayıcı oldu. En yakın arkadaşım vefat etti. Sıkıntılı ve zor süreçlerdi." (K10)

Yetersizlik

Katılımcılar hastaları ile benzer acıları yaşadıklarını ve onları iyileştirme noktasında kendilerini yetersiz hissettiklerini belirtmişlerdir.

"Benzer süreçleri yaşadığımız için bazen destek vermekte yetersiz kaldığımı hissettiğim oldu. Hasta ile ağladım. Benim zayıf yönümü gördüğü için kendimi yetersiz hissettim" (K2)

"Öte yandan gerek tanıdığım bildiğim insanların gerekse diğer insanların yaşadıkları olumsuzlukları görmek dinlemek çok zor bir tecrübe. İlk süreçte bu duygular yoğun bir şekilde etrafımı sardı, işlevselliğimi etkiledi. Kendime bile faydam olmadığını hissettim." (K13)

Suçluluk

Katılımcılar hastalarının deprem travması sonrası kendilerinden daha ağır şeyler yaşadıklarını dinleyince suçluluk hissettiklerinden bahsetmişlerdir.

"Ağır şeyler yaşayan hastaları gördükçe kendi yaşadıklarımı onların acıları ile kıyaslayıp kendimi suçladım." (K5)

"Hayatta olduğum ve ailemi kaybetmediğim için hastadan daha iyi durumda olduğum için kendimi suçlu hissettim." (K15)

***Davranışsal tepkiler*:** Katılımcılar yaşadıkları travmadan sonra hastalarının travma anlatıları karşısında aşırı uyarıldıklarını ve hastalarının anlattıklarına karşı kaçınma davranışı sergilediklerini ifade etmişlerdir.

Aşırı uyarılma

Katılımcılar hastaları ile yaptıkları görüşmelerde hastalarının anlattıklarına karşı depreme yönelik en ufak bir belirtiye dair aşırı uyarılma halinde olduklarını belirtmişlerdir.

"Ya bende enkaz altında kalsaydım aileme bir şey olsaydı diye düşündüğümde elimde olmadan gözlerim doldu. Hastaların hikayelerinde depremde yaşadıklarım aklıma geldikçe daha kötü hissettim kendimi. Hastalar ile kurduğum her temas beni aşırı tetikledi." (K14)

Kaçınma

Katılımcılar deneyimledikleri travmatik olayı hatırlatan uyarıcılardan kaçınmaya çalıştıklarını ve düşünmemeye çalıştıklarını ifade etmişlerdir:

"Hastalar anlatmaya başladığında konuyu kısa kesmeye çalıştım. Onların anlattıklarında kendi hikayeme benzer şeyler buldum. Bunları dinlemek istemediğimi fark ettim. Kaçınma davranışı gösterdiğimi anladım"(K9)

"Artık travma hastası görmek istemediğimi fark ettim. Onlara faydalı olmak istiyordum ama acılarına tekrar tekrar şahitlik yapmak istemiyordum." (K16)

3.3. Afet bölgesinde yaşanılan zorluklar

Katılımcılar deprem bölgesinde hem yaşarken hem de ruh sağlığı hizmeti verirken temel ihtiyaçların karşılanmaması ve iş yükünün artmasından dolayı zorlandıklarından bahsetmişlerdir. Depremden dolayı fiziksel ihtiyaçlarını karşılama noktasında dahi zorlandıklarını ifade etmişlerdir. Ayrıca katılımcılar da birer travma mağduru iken çok fazla travma hastasının başvurmasının iş yüklerini arttırdığını belirtmişlerdir. Bu zorluklara ilişkin alt kategoriler aşağıda katılımcı görüşmeleri ile yer almaktadır:

Temel ihtiyaçların karşılanamaması: Deprem şehrin alt yapısını yıktığı için katılımcılar özel ve iş hayatlarında en temel ihtiyaçlarını karşılama noktasında dahi zorlandıklarını ve bu durumun mesleki yaşantılarını olumsuz etkilediklerinden bahsetmişlerdir:

"Kişinin istediği düzeyde performans sergilemesinin önünde birçok sorunun olduğunu, gerekli fiziksel koşullar sağlanmadığını, barınma sorununun kısmen devam etmesi, sosyal yaşama dair etkinliklerin çok kusurlu olması, birçok meslek gurubunda halen eksikliklerin karşılanamaması gibi sorunlardan dolayı çalışma hayatında eksikliklerin devam edeceğini düşünmekteyim. İş yükünün zamanla artmaya başladığı, özellikle sağlık alanında personel yetersizliği baş göstereceğini, bu alanlarda iyileştirme sürecinin bireylerde ruhsal ve fiziksel şikayetlerin artacağını düşünmekteyim." (K3)

"Güvenli bir kalacak yer, tuvalet, ısınma gibi en temel ihtiyaçlarımızı nasıl karşılayacağımıza dair endişeler bizi bu süreçte çok zorladı. Sürekli artçı depremlerin olması bizim iyileşmemizi zorlaştırdı." (K8)

"Çok fazla hasta geldi, herkes travma destek birimlerine başvurdu. Çünkü herkes çok kötüydü. Görüşmeleri yapacak sağlam bir yer bulmakta dahi zorlandık." (K12)

İş yükü artması: Katılımcılar kısıtlı imkanlarla çalıştıklarını ve deprem sonrasında psikiyatri bölümüne çok fazla hasta başvurusu olduğu ve başvuran hastaların profillerinin kötü olduklarından bahsetmişlerdir. Bu doğrultuda iş yükünün artmasına yönelik görüşler aşağıda belirtilmektedir:

"İlk başta hastaneler riskli diye çadırlarda ruh sağlığı hizmeti vermeye devam ettik ancak başvuran hasta sayısı çok, hasta profilleri kötü ve eldeki imkanlar kısıtlıydı."

"Kliniğe başvuran hastalar yakınlarının zorlaması ile başvurmuşlardı ve katatoni gibi asla iletişim kurmuyorlardı. Gelen hastaların profili çok ağırdı. İntihar etmek istediğini belirten çok hasta vardı. O kadar çok bakacak hasta vardı ki."

3.4. Travma ile baş etme

Katılımcılar depremden sonra bölgeye yapılan yardımların ve çevrelerindeki ve hatta hiç tanımadığı insanlardan aldıkları desteğin kendilerini iyi hissetmelerini sağladığını belirtmişlerdir. Ancak yaşadıkları travma ile baş etmeye çalışırken ilaç kullanımlarında artış olduğunu da ifade etmişlerdir. Katılımcıların travma ile baş etmeye yönelik ifadelerinin sosyal destek ve ilaç kullanımında artış çevresinde şekillendiği belirlenmiştir.

Sosyal destek alma: Katılımcılar aile, çevre ve hatta hiç tanımadıkları insanlardan destek aldıkça kendilerini daha iyi hissettiklerini ve motive olduklarını ifade etmişlerdir.

"Bölgede benzer duyguları yaşadığımız insanlarla ortak zaman geçirmek, rutine dönmeye gayret etmek iyi geldi. Sosyal destek ve mesleki destek bulmak daha dayanıklı hissettirdi hatta yardım için gönderilen bir çorap bile sıcak tuttu diye sevindim." (K2)

"Arkadaşlarımla daha çok zaman geçirerek kendimi korumaya çalışıyorum. Sevdiklerimle bir ardada olunca dayanıklılığımın arttığını düşünüyorum." (K8)

İlaç kullanımında artış: Katılımcıların çoğunluğu depremden sonra travma stresi ile baş etmek için ilaç kullanmaya başladıklarını ifade etmişlerdir.

"Depremden yaklaşık 2 ay sonra antidepresan kullanmaya başladım (Fluoksetin 20 mg). Hala tedaviye devam ediyorum." (K17)

"İlaç kullanımım arttı. Antidepresan ve uyku ilaçları alıyorum." (K5)

3.5. Travma sonrası büyüme

Çalışmada yer alan ruh sağlığı profesyonelleri depremden sonra travmaya yaklaşım konusunda kendilerini geliştirmek istediklerinden ve hayata bakış açılarında pozitif bir değişimin olduğundan bahsetmişlerdir. Travma sonrası katılımcılarda gelişen bu pozitif bakış açısı travma sonrası büyüme olarak yorumlanmıştır. Buna yönelik kategori ve görüşme örnekleri aşağıda belirtilmektedir:

Hayata bakış açısı: Katılımcılar deprem travmasından sonra hayata bakış açılarında olumlu anlamda bir gelişme olduğundan ve hayatın her şeye rağmen devam ediyor olmasına yönelik olumlu düşüncelerinin olduğunu ifade etmişlerdir.

"Uzun vadeli planlar yapmamaya başladım. Sevdiğim insanların her an aramızdan ayrılabileceğini düşündüm. En yakın arkadaşımı kaybettim. Evimiz yıkıldı. O evden sağ çıktığımız için şükrediyorum." (K10)

"Depremden dolayı hayata bakış açım çok değişti. Üzüldüm, ağladım, aylarca düzgün uyuyamadım ancak şimdi değerlendirdiğimde hayatı yaşanan acıdan kaçmaya çalışmadan değerlerim doğrultusunda erdemli bir şekilde yaşamak istediğimi, yaşanmış onca acının bana bunu hatırlattığını düşündüm." (K6)

"Yaşamla ve doğayla olan ilişkimi yeniden gözden geçirmemi sağladı. Hayatta değerli olduğunu düşündüğüm kişi ve etkinliklere daha çok zaman ayırmaya başladım." (K2)

Travma ile etkin baş etmede kendini geliştirmek: Katılımcılar hastalar ile çalışırken zorlandıklarını ancak yaşadıkları benzer travmaların hastaları daha iyi anlamalarına yardımcı olduğundan ve travmaya nasıl müdahale edileceğine dair daha çok literatür okumaları yaptıklarından bahsetmişlerdir. Buna yönelik katılımcı ifadeleri:

"Yaptığım işin insanların yaşamları üzerindeki etkilerini ve sağlayabileceği faydaları değerlendirdikten sonra, eksik olduğumu düşündüğüm alanlarda araştırmalar yaparak ve meslektaşlarımdan destek alarak kişisel gelişim sürecimi sürdürmeye özen gösteriyorum." (K3)

"O kadar çok travma hastasına bakıyoruz ki şuan travma hastasına yaklaşımda çok fazla deneyim kazandım." (K9)

4. Tartışma

Bu çalışmada toplumsal travmaya maruz kalmış ruh sağlığı profesyonellerinin paylaşılan travmatik gerçeklik ve baş etme deneyimleri incelenmiştir. Araştırmacılar katılımcıların anlatılarından elde edilen bulguları analiz etmiş ve beş ana kategori belirlemiştir.

4.1. Paylaşılan travmatik gerçeklik

Ruh sağlığı profesyonelleri ile yapılan görüşmelerin temelinde kendilerinin de birer travma mağduru olduklarından ve hastaları ile aynı travmaları yaşadıklarından bahsetmişlerdir. Kolektivist değerlere ve kolektif travma geçmişine sahip toplumlarda paylaşılan travma kavramı çok az dikkate alınmış olup genellikle batı toplumlarında ele alınmıştır (40). Paylaşılan travmatik gerçeklik ile ilişkili COVID-19 pandemi döneminde Kanada ve Amerika Birleşik Devletleri'nde ruh sağlığı klinisyenleri arasında paylaşılan travmatik gerçeklik kavramının araştırıldığı bir çalışmada klinisyenlerin pandeminin psikososyal etkilerini bireysel olarak deneyimlediklerini ancak danışanları ile olan ilişkilerinde profesyonel ilişkilerini etkilemediği sonucunu paylaşmışlardır (41). COVID-19 döneminde hastalarla olan fiziksel temasın sınırlandırıldığı ve görüşmelerin genellikle uzaktan erişim ile yapıldığı dönemler göz önüne alınırsa

(42), bu çalışmada yer alan katılımcılar depremi doğrudan yaşadıkları için paylaşılan travmatik gerçeklik karşısında daha olumsuz etkilenmelerini makul bir zeminde açıklayabilir. Bu katılımcılar paylaşılan travmatik gerçeklik karşısında tükenmişlik, yoğun özdeşim, çifte maruziyet ve travmatik karşı aktarım yaşadıklarından bahsetmişlerdir. Ruh sağlığı profesyonelleri ile hastaların aynı travmatik gerçekliği paylaştığı durumlar için kullanılan paylaşılan travmatik gerçeklik kavramı terapötik ilişkide olumlu veya olumsuz sonuçlara yol açabilir (41). Nitekim alan yazında paylaşılan travmatik gerçeklik kavramı Katrina Kasırgası (43), çatışma bölgelerinde yaşanan savaşlardan sonra (44) ve COVID-19 döneminde araştırılmış olup (41) deprem travmasına bağlı paylaşılan travmatik gerçeklik kavramının ruh sağlığı profesyonellerinde araştırılmadığı saptanmıştır. Paylaşılan travmatik gerçeklik karşısında klinisyenler çaresizlik, üzüntü, yetersizlik ve suçluluk duygusunu daha yoğun hissettiklerinden bahsetmişlerdir. Travmatik olaylar insanların bağ kurma, kontrol etme ve duygusal sistemlerini alt üst eder. Paylaşılan travmatik gerçeklikte ruh sağlığı profesyoneli hastasının yaşadığı duygular karşısında acı, caresizlik gibi duyguları hissedebilir (9).

4.2. Travmaya karşı tepkiler

Katılımcılar yaşadıkları travma sonrası üzüntü, çaresizlik yetersizlik ve suçluluk gibi duyguları daha yoğun yaşadıklarını, aşırı uyarılma ve kaçınma davranışı sergilediklerini ifade etmişlerdir. Sığınmacılar ve mülteciler ile çalışan tercümanların maruz kaldıkları travma sonrası öfke, umutsuzluk, çaresizlik, korku, kaygı ve derin üzüntü gibi olumsuz duyguları yaşarken sevinç, umut, hayranlık, ilham, danışanın iyileşmesine tanıklık etme ve daha derin ve daha anlamlı bir yaşam yaşama arzusu gibi olumlu kazanımlar elde ettikleri bildirilmiştir (45). Başka bir çalışmada travma yaşayan kurbanlarla empatik ilgilenen ruh sağlığı profesyonellerinde keder, öfke gibi ciddi duygusal tepkiler raporlanmıştır (46). Travma mağdurları ile çalışmanın ruh sağlığı profesyonelleri üzerinde olumsuz duygusal etkilerinin olmasında mağdurların travmalarına doğrudan veya dolaylı olarak tanık olmanın etkisinin olabileceği çıkarımında bulunulabilir. Savaş ortamında çalışan terapistler ile yapılan araştırmalar sonrasında doğrudan ve dolaylı olarak travmaya maruz kalan terapistlerin yaşadıkları travma sonrası üzüntü, kayıp, korku, acı ve keder, tehdit, belirsizlik ve hatta bazen çaresizlik duygularını tanımladıkları belirtilmiştir (47, 48). Savaş ya da doğal afet gibi travmatik bir olay sonrasında hastaları ile benzer travmaları yaşayan ruh sağlığı profesyonellerinin yaşanılan travmaya benzer tepkiler gösterebileceği ifade edilebilir. Kurşun ve arkadaşlarının ruh sağlığı profesyonelleri ile yapmış oldukları çalışmada kendilerinin de danışanları gibi pandemi döneminde benzer süreçleri yaşadıkları için çifte maruziyete maruz kaldıkları ve kendilerini yetersiz ve çaresiz hissettikleri belirtilmiştir (49). Travma mağdurları ile benzer travmalara maruz kalan bireylerin travmaya karşı benzer tepkiler geliştirdikleri görülmektedir.

4.3. Afet bölgesinde yaşanan zorluklar

Bu çalışmada yer alan bireyler deprem bölgesinde hem yaşarken hem de çalışırken temel ihtiyaçlarını karşılamada ve iş yükü artışlarından dolayı zorluklar yaşadıklarını belirtmiştir. Deprem bölgesinde alt yapının zarar görmesi, fiziksel ihtiyaçlar noktasında beslenme, boşaltım ve güvenlik gibi ihtiyaçlarda yaşanılan zorlanmalar travma mağdurlarının mağduriyet düzeylerini arttırabilir. İhtiyaçların karşılanmasında yaşanılan zorluklar travmatik süreçlerin başarı ile atlatmasını zorlaştırabilir. Yaşanılan zorluklar ruh sağlığı profesyonellerinin travma sonrası büyümeyi yakalamalarını zorlaştırabilir. Travma sonrası büyüme; çevresel (travma stres düzeyi, sosyal destek, sosyokültürel etkiler) ve bireysel özellikler (kişilik özellikleri, stres yönetimi, baş etme mekanizmaları, duygusal kendini açma) gibi çeşitli faktörlerden etkilenmektedir (50). Yaşanılan bu zorlukların tersine bireyler akran desteği, takım çalışması, sevdiklerinin yanlarında olması, olumlu telkin, maneviyat gibi olumlu pekiştireçler bireylerin travma sonrası büyümeyi yakalamalarını kolaylaştırabilir. Ruh sağlığı profesyonellerinin aldıkları uzmanlık eğitimi, mesleki deneyimleri ve akran desteği bu meslek grubunu dolaylı travmatizasyona karşı koruyabilir. Ayrıca mesleki öz yeterlilik duygusu, hastaları tedavi etme isteği ve mesleki beceriler de dolaylı travmatizasyona karşı tampon görevi görüp travma sonrası büyümeyi teşvik edebilir ve hastaları ile olan ilişkilerini daha olumlu anlamda etkileyebilir (13, 51). Çalışma ortamında şartların iyileştirilmesi ruh sağlığı profesyonellerini olumlu anlamda motive edebilir.

4.4. Travma ile baş etme

Bir diğer bulgu olarak çalışmada yer alan ruh sağlığı profesyonelleri yaşadıkları travmatik süreç ile baş etme yöntemleri olarak ilaç kullanımında artış olduğunu ve sosyal destek almanın kendilerini motive ettiklerinden bahsetmişlerdir. Olumsuz

yaşam olaylarının oluşturduğu stresle başa çıkma sürecinde insanlar bastırma, yansıtma gibi savunma mekanizmaları ya da öfke duyma gibi duygusal boyutta, yürüyüş, egzersiz yapma, ibadete yönelme gibi davranışsal boyutta çabalar gösterebilmektedir (52). Finklestein ve arkadaşları hastaları ile aynı travmatik yaşantılara doğrudan maruz kalan ruh sağlığı profesyonellerinin aynı travmatik yaşantılara doğrudan maruz kalmayan ruh sağlığı profesyonellerine göre birincil ve ikincil travma düzeylerinin daha yüksek olduğunu, stres ile başa çıkmada daha savunmasız olabileceği, mesleki öz yeterliliklerine ilişkin kendilerini daha çaresiz hissettikleri belirtilmiştir (13). Bu bağlamda doğrudan ve dolaylı olarak travmaya maruz kalan bireylerin bireysel iyi oluşları baş etme mekanizmalarını olumlu etkileyebilir.

4.5. Travma sonrası büyüme

Katılımcılar yaşanılan deprem felaketinden olumsuz etkilendiklerini ancak bazı alanlarda kendilerinde olumlu gelişmeler hissettiklerini belirtmişlerdir. Aynı ve benzer acıları yaşadıkları mağdurların ve kendilerinin refahı için travmayı iyileştirmede daha çok araştırmalar yaptıklarını, kendilerini geliştirmek istediklerini, yaşanılan olumsuz süreçlerden öğrenerek çıktıklarını ifade etmişlerdir. Ayrıca kişisel gelişim için çaba gösterdiklerini, sevdiklerine daha çok zaman ayırmak istediklerini ve hayata bakış açılarının geliştiğini belirtmişlerdir. Literatür incelemesinde travma çalışanları yaşadıkları dolaylı travma sürecini başarılı bir şekilde yönetebilirlerse travma sonrası büyüme düzeyini yakalayabilecekleri bildirilmektedir (53, 54). Travma çalışanlarının travma sonrası büyüme düzeyini yakalayabilmesi için bazı parametrelerin teşvik edilmesi gerektiğine dair bir anlayış bulunmaktadır (örneğin; çalışma koşullarını iyileştirilmesi, terapötik sonuçlar, mesleki rolün korunması gibi) (45, 55). Kurşun ve arkadaşlarının yaptığı çalışmada zorlu gruplarla çalışan ruh sağlığı profesyonellerinin psikolojik ilk yardım, kriz yönetimi ve kritik müdahalelerde bulunmaya yönelik danışmanlık ve süpervizyon almaya ihtiyaçlarının olduğu belirtilmiştir (49). Yaşanılan doğrudan ve dolaylı travma sonrası ruh sağlığı profesyonellerinin olumlu yönde desteklenmesi yaşanılan olumsuz süreçlerin olumlu yöne kanalize edilmesini sağlayabilir, böylelikle travma sonrası büyüme yaşanabilir.

5. Sonuç

Araştırmada yer alan ruh sağlığı profesyonelleri toplumsal travma yaşadıkları için paylaşılan travmatik gerçeklik yaşadıklarından bahsetmişlerdir. Yaşanılan paylaşılan travmatik gerçeklik karşısında hastaları ile görüşmeleri sırasında travmatik karşı aktarım, çifte maruziyet, özdeşim ve tükenmişlik yaşadıklarını ifade etmişlerdir. Hastaları ile aynı travmayı yaşamanın bir sonucu olarak çaresizlik, üzüntü, yetersizlik, suçluluk gibi duygusal tepkiler yaşadıklarından ve aşırı uyarılma ve kaçınma davranışı gösterdiklerinden bahsetmişlerdir. Görevlerini gerçekleştirirken çok fazla travma yaşayan hasta başvurusu sonucu iş yüklerinin arttığı ve deprem bölgesinde hizmet vermeye çalışırken temel ihtiyaçlarını karşılama noktasında dahi zorluklar yaşadıkları sonucuna ulaşılmıştır. Deprem bölgesinde çalışmaya devam ederken aldıkları sosyal destekler sayesinde kendilerini iyi hissettiklerini ancak yine de yaşanılan travmanın etkisi ile baş etmede ilaç kullanımlarının da olduğu sonucu elde edilmiştir. Ruh sağlığı profesyonelleri yaşadıkları travma ve hastalarının travmalarına maruziyet sonrası travma ile daha etkin baş edebilmek için daha fazla okumalar yaptıklarından bahsetmişlerdir. Ayrıca yaşanılan travmanın hayata bakış açılarında olumlu bir gelişim yaptığını ifade etmişlerdir.

Ruh sağlığı profesyonellerinin özellikle toplumsal travmalara karşı veya paylaşılan travmatik gerçekliğe yönelik uzmanlık eğitimi ile desteklenmesi bireyleri travmanın olumsuz etkilerine karşı koruyabilir. Paylaşılan travmatik gerçekliğin ruh sağlığı profesyonellerinin hastaları ile olan ilişkilerine olumsuz yansımaması için bu meslek gruplarının afet, savaş, göç gibi toplumsal travmalara karşı desteklenmelerinin önemli olacağı düşünülmektedir. Sonuç olarak hastaları ile ortak travma yaşama riskinden dolayı ruh sağlığı profesyonellerinin toplumsal travmalara karşı desteklenmesi önerilmektedir.

Araştırmanın Sınırlılıkları ve Güçlü Yönleri: Depremden sonraki süreçlerde nicel bir çalışma için yeterli örneklem büyüklüğüne ulaşılamayacağı ayrıca paylaşılan travmatik gerçeklik kavramını ölçecek bir ölçüm aracı olmadığı için bu çalışmada nitel araştırma yöntemi kullanılmıştır. Bu durum çalışmanın nicel veriler ile desteklenmemesi sonucundan dolayı çalışmanın sınırlılığını oluşturabilir.

Araştırmanın örneklem grubunu oluşturan bireylerin hem deprem bölgesinde doğrudan depremi yaşayan deprem mağduru olmaları hem de ruh sağlığı hizmeti veren meslek üyeleri olması bu çalışmanın güçlü yanını oluşturmaktadır. Bu örneklem grubunun özellikle seçilmesine gerekçe olarak hastaları ile ortak travma yaşama deneyimine yönelik literatüre katkı sağlanmak istenmiştir.

Ayrıca çalışmada yer alan ruh sağlığı profesyonellerinin psikiyatrist, psikiyatri hemşireleri ve psikolog gibi farklı meslek gruplarından oluşması çeşitli deneyimlere ve görüşlere erişilmesini sağlayarak geniş bir katılımcı yelpazesinin olmasına önem gösterilmiştir.

Gelecek çalışmalara öneriler

Dünyada ve Türkiye'de gittikçe artan toplumsal travmalar toplumların ruh sağlığını etkilemekte ve toplumun birer üyesi olan ruh sağlığı profesyonellerini de etkilemektedir. Toplumsal travmalardan etkilenen ruh sağlığı profesyonellerinin travma deneyimlerinin mesleki yaşantılarına nasıl yansıdığı ve bu konudaki deneyimlerinin belirlenmesinin önemli olduğu düşünülmektedir. Nitekim toplumsal travmalarda genellikle travma sonrası stres bozukluğu ve ikincil travma gibi kavramlar ele alınmış olup paylaşılan travmatik gerçeklik kavramının araştırılmasına ihtiyaç duyulmuştur. Bu ihtiyaç doğrultusunda paylaşılan travmatik gerçeklik kavramının nicel araştırmalar çerçevesinde tespit etmeye yönelik bir ölçüm aracının geliştirilmesi önerilmektedir. Paylaşılan travmatik gerçeklik yaşadığı kabul edilen ruh sağlığı profesyonellerinin hastaları ile olan görüşmelerine bu durumun yansıyıp yansımadığının araştırılması önerilmektedir. Ruh sağlığı profesyonellerinin toplumsal travmalara karşı dayanıklılıklarının arttırılması konusunda güçlendirilmeleri ve gerekli beceriler ile donanımlarının arttırılmasına yönelik girişimsel çalışmaların yapılmasının alana katkı sağlayacağı düşünülmektedir.

KAYNAKLAR

1. Hoffman MA, Kruczek TA. Bioecological model of mass trauma: Individual, community, and societal effects. The Counseling Psychologist. 2011;39(8):1087-1127.
2. Bilewicz M, Witkowska M, Pantazi M, Gkinopoulos T, Klein O. Traumatic rift: How conspiracy beliefs undermine cohesion after societal trauma? Europe's Journal of Psychology. 2019;15(1):82.
3. Liu H, Tatano H, Pflug G, Hochrainer-Stigler S. Post-disaster recovery in industrial sectors: A Markov process analysis of multiple lifeline disruptions. Reliability Engineering & System Safety. 2021;206:107299.
4. Yang Y, Tatano H, Huang Q, Liu H, Yoshizawa G, Wang K. Evaluating the societal impact of disaster-driven infrastructure disruptions: A water analysis perspective. International Journal of Disaster Risk Reduction. 2021;52:101988.
5. Karatay G. Tarihsel/toplumsal travmalar ve kuşaklararası aktarımı biçimleri üzerine. Sürekli Tıp Eğitimi Dergisi. 2020;29(5):373-379.
6. Figley CR, Beder J. (Edited by). The cost of caring requires self care. In Advances in social work practice with the military. Routledge, 2012: 278-286.
7. García FE, Cova F, Rincón P, Vázquez C. Trauma or growth after a natural disaster? The mediating role of rumination processes. European Journal of Psychotraumatology. 2015;6(1):26557.
8. Işıkhan V. Afetlere müdahale eden yardım personelini güçlendirme. Doğal Afetler ve Çevre Dergisi. 2021;7(2):399-406.
9. Kanno H. Supporting indirectly traumatized populations: The need to assess secondary traumatic stress for helping professionals in DSM-V. Health and Social Work. 2010;35(3): 225-228.
10. Lerias D, Byrne MK. Vicarious traumatization symptoms and predictors. Stress Health: Journal of the International Society for the Investigation of Stress, 2003;19(3):129–138.
11. Tosone C, Nuttman-Shwartz O, Stephens T. Shared trauma: When the professional is personal. Clinical Social Work Journal. 2012;40(2):231–239.
12. Baum N. Shared traumatic reality in communal disasters: Toward a conceptualization. Psychotherapy: Theory, Research, Practice, Training. 2010;47(2):249–259.
13. Finklestein M, Stein E, Greene T, Bronstein I, Solomon Z. Posttraumatic stress disorder and vicarious trauma in mental health professionals. Health & Social Work. 2015;40(2):e25-e31.
14. Freedman SA, Tuval Mashiach R. Shared trauma reality in war: Mental health therapists' experience. PloS one. 2,08;13(2):e0191949.
15. Dekel R, Nuttman-Shwartz O, Lavi T. Shared traumatic reality and boundary theory: How mental health professionals cope with the home/work conflict during continuous security threats. Journal of Couple & Relationship Therapy. 2016;15(2):121-134. doi.org/10.1080/15332691.2015.1068251
16. Ludick M, Figley CR. Toward a mechanism for secondary trauma induction and reduction: Reimagining a theory of secondary traumatic stress. Traumatology. 2017;23(1):112.
17. Naushad VA, Bierens JJ, Nishan KP, Firjeeth CP, Mohammad OH, Maliyakkal AM, ..., Schreiber MD. A systematic review of the impact of disaster on the mental health of medical responders. Prehospital and disaster medicine. 2019;34(6):632-643.
18. Calhoun CD, Stone KJ, Cobb AR, Patterson MW, Danielson C K, Bendezú JJ. The role of social support in coping with psychological trauma: An integrated biopsychosocial model for posttraumatic stress recovery. Psychiatric Quarterly. 2022;93(4):949-970.
19. Day KW, Lawson G, Burge P. Clinicians' experiences of shared trauma after the shootings at Virginia Tech. Journal of Counseling & Development. 2017;95(3):269-278.

20. Dursun P, Söylemez İ. Travma sonrası büyüme: Gözden geçirilmiş son model ile kapsamlı bir değerlendirme. Türk Psikiyatri Dergisi. 2020;31(1):57-68.
21. De Ruiter MC, Couasnon A, van den Homberg MJ, Daniell JE, Gill JC, Ward PJ. Why we can no longer ignore consecutive disasters. Earth's Future. 2020;8(3):e2019EF001425.
22. Dinçer İ, Akın MK, Akın M, Orhan A, Ozan O, Varol MB, Benlioğlu TB. 6 Şubat 2023 Kahramanmaraş depremleri. Konuralp Medical Journal. 2023;14(1):1-16.
23. Sağıroğlu AZ, Ünsal R, Özenci F. Deprem sonrası göç ve insan hareketlilikleri: durum değerlendirme raporu (AYBÜ-GPM, 2023). Güncellenmiş 2. Baskı, 2023;1-44:5.
24. Yıldız Mİ, Başterzi AD, Yıldırım EA, Yüksel Ş, Aker AT, Semerci B, ..., Hacıoğlu Yıldırım M. Preventive and therapeutic mental health care after the earthquake- expert opinion from the psychiatric association of Turkey. Turkish Journal of Psychiatry. 2023;34(1):39-49.
25. Sehlikoğlu Ş, Yilmaz Karaman IG, Yastıbaş Kaçar C, Canakci ME. Earthquake and mental health of healthcare workers: A systematic review. Turkısh Journal Clınıcal Psychıatry. 2023;26(4):309-318.
26. Baltacı A. Nitel araştırma süreci: Nitel bir araştırma nasıl yapılır? Ahi Evran Üniversitesi Sosyal Bilimler Dergisi. 2019; 5(2): 368-388.
27. Demirtepe-Saygılı D. Refleksivite ve etkileşim açılarından nitel araştırmacı olmanın fırsatları ve zorlukları. AYNA Klinik Psikoloji Dergisi. 2021;8(1):1-16.
28. Borrego M, Douglas EP, Amelink CT. Quantitative, qualitative, and mixed research methods in engineering education. Journal of Engineering Education. 2009;98(1):53-66.
29. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77–101.
30. Braun V, Clarke V. Novel insights into patients' life-worlds: the value of qualitative research. Lancet Psychiatry. 2019;6(9):720–1. doi.org/10.1016/
31. Dereli AB. MAXQDA: Technıcal note on creatıve data analysıs. Journal of Karadeniz Communication Studies. 2023;13(1):149-152.
32. Baltacı A. Nitel araştırmalarda örnekleme yöntemleri ve örnek hacmi sorunsalı üzerine kavramsal bir inceleme. Bitlis Eren Üniversitesi Sosyal Bilimler Dergisi. 2018;7(1):231-274.
33. Kretsch R, Benyakar M, Baruch E, Roth M. A shared reality of therapists and survivors in a national crisis as illustrated by the Gulf War. Psychotherapy: Theory, Research, Practice, Training. 1997;34(1):28.
34. Saakvitne KW. Shared trauma: The therapist's increased vulnerability. Psychoanalytic Dialogues. 2002;12(3):443-449.
35. Şad SN, Özer N, Atli A. Psikolojide tematik analizin kullanımı. Eğitimde Nitel Araştırmalar Dergisi. 2019;7(2):873-898.
36. Tekindal M, Arsu ŞU. Nitel araştırma yöntemi olarak fenomenolojik yaklaşımın kapsamı ve sürecine yönelik bir derleme. Ufkun Ötesi Bilim Dergisi. 2020;20(1), 153-172.
37. Tong A, Saınsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. International Journal for Quality in Health Care. 2007;19(6):349-357.
38. Nowell LS, Norris JM, White DE, Moules NJ. Thematic analysis: Striving to meet the trustworthiness criteria. Int J Qual Methods. 2017;16(1):1609406917733847.
39. Yaşar M. Nitel araştırmalarda nitelik sorunu. Muğla Sıtkı Koçman Üniversitesi Eğitim Fakültesi Dergisi. 2018;5(2):55-73.
40. Ali DA, Figley CR, Tedeschi RG, Galarneau D, Amara S. Shared trauma, resilience, and growth: A roadmap toward transcultural conceptualization. Psychological Trauma: Theory, Research, Practice, and Policy. 2023;15(1):45.
41. Asakura K, Gheorghe RM, Rieger D, Tarshis S, Borgen S, D'Angiulli A. Exploring shared trauma in the time of COVID: A simulation-based survey study of mental health clinicians. Clinical Social Work Journal. 2023;51(2):163-174.
42. Holmes MR, Rentrope CR, Korsch-Williams A, King JA. Impact of COVID-19 pandemic on posttraumatic stress, grief, burnout, and secondary trauma of social workers in the United States. Clinical Social Work Journal. 2021;49(4):495–504.
43. Tosone C, McTighe JP, Bauwens J. Shared traumatic stress among social workers in the aftermath of Hurricane Katrina. British Journal of Social Work. 2015;45(4):1313-1329.
44. Dekel R, Baum N. Intervention in a shared traumatic reality: A new challenge for social workers. British Journal of Social Work. 2010;40(6):1927-1944.
45. Splevins KA, Cohen K, Joseph S, Murray C, Bowley J. Vicarious posttraumatic growth among interpreters. Qualitative health research. 2010;20(12):1705-1716.
46. Figley CR, Ludick M. Secondary traumatization and compassion fatigue. In S. N. Gold (Edited by), APA handbook of trauma psychology: Foundations in knowledge. American Psychological Association. 2017:573-593.
47. Baum N. Professionals' double exposure in the shared traumatic reality of wartime: Contributions to professional growth and stress. The British Journal of Social Work. 2014;44(8):2113-2134.
48. Cohen M, Gagin R, Peled-Avram M. Multiple terrorist attacks: Compassion fatigue in Israeli social workers. Traumatology. 2006;12(4):293-301.
49. Kurşun GŞ, Uygun E, Dikeç G. The experiences of mental health professionals providing online psychological support to refugees during the COVID-19: A qualitative study. J Cogn Behav Psychother Res. 2023;12(3):264-278.
50. Duman N. Travma sonrasi büyüme ve gelişim. Uluslararası Afro-Avrasya Araştırmaları Dergisi. 2019;4(7):178-184.
51. Kanno H, Giddings MM. Hidden trauma victims: Understanding and preventing traumatic stress in mental health professionals. Social Work in Mental Health. 2017;15(3):331-353.
52. Gören AB. Postdisaster secondary traumatic stress and religious coping: The case of Kahramanmaraş Earthquake. Turkish Journal of Religious Studies. 2023;23(1):80-100.
53. Chen R, Sun C, Chen JJ, Jen HJ, Kang XL, Kao CC, Chou KR. A large-scale survey on trauma, burnout, and posttraumatic growth among nurses during the

COVID-19 pandemic. International Journal of Mental Health Nursing. 2021;30(1):102-116.
54. Vazquez C, Valiente C, García FE, Contreras A, Peinado V, Trucharte A, Bentall RP. Posttraumatic growth and stress-related responses during the COVID-19 pandemic in a national representative sample: The role of positive core beliefs about the world and others. Journal of Happiness Studies. 2021;22 (1):2915–2935.
55. McCann IL, Pearlman LA. Vicarious traumatization: A framework for understanding the psychological effects of working with victims. Journal of Traumatic Stress. 1990;3:131-149.

Osmangazi Journal of Med, 2025;47(1): 85-90
DOI: 10.20515/otd.1584127

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

The Effect of Internet Addiction on Preoperative Anxiety in Adolescent

Ergenlerde İnternet Bağımlılığının Preoperatif Anksiyete Üzerine Etkisi

Nuran Akıncı Ekinci, Mehmet Akif Yazar, Aydın Mermer, Rabia Korkmaz

University of Health Sciences, Konya City Hospital, Department of Anesthesiology and Reanimation, Konya, Türkiye

ORCID ID of the authors
NAE. 0000-0003-3269-3481
MAY. 0000-0002-3415-1363
AM. 0000-0002-9859-4737
RK. 0009-0003-4283-7546

Correspondence / Sorumlu yazar:
Nuran AKINCI EKİNCİ

University of Health Sciences, Konya City Hospital, Department of Anesthesiology and Reanimation, Konya, Türkiye

e-mail: nurandr@yahoo.com

Abstract: Internet addiction has been associated with mental health issues such as anxiety, sleep disorders, and depression in adolescents. However, its effects on preoperative anxiety have not been adequately studied. Our goal is to investigate the consequences of internet addiction on preoperative anxiety in adolescents undergoing surgery. The study was carried out by the approval of the Karatay University Ethics Committee at Konya City Hospital between August and December 2023. A total of 150 patients aged 12–18 who would undergo general anesthesia were included. Preoperative anxiety was evaluated utilizing the "Spielberger State-Trait Anxiety Inventory" (STAI-1), and internet addiction was assessed using the "Young Internet Addiction Scale" (IAS). Statistical analyses were performed using SPSS, and Pearson correlation, ANOVA, and regression analyses were used. It was found that 45.3% of the patients were internet addicts, and this group experienced higher levels of preoperative anxiety ($r = 0.728$, $p<0.01$). Pairwise comparisons revealed statistically significant differences among all groups. We observed a strong positive connection between internet addiction and preoperative anxiety. Additionally, it was observed that age and easy access to the internet increased anxiety levels, with individuals having more accessible access to the internet experiencing higher anxiety levels compared to those with limited access ($\beta = 0.189$, $p = 0.018$). Internet addiction is an important factor that increases preoperative anxiety levels in adolescents undergoing surgery. Age and ease of internet access are other variables affecting anxiety levels. These findings suggest that internet addiction should be taken into account during preoperative processes.
Keywords: Internet addiction, Preoperative anxiety, Adolescents, General anesthesia

Özet: Bu çalışma, cerrahi geçirecek ergenlerde internet bağımlılığının preoperatif anksiyete üzerindeki etkilerini araştırmayı amaçlamaktadır. İnternet bağımlılığı ergenlerde anksiyete, uyku bozuklukları ve depresyon gibi ruhsal sorunlarla ilişkilendirilmiştir. Ancak, preoperatif anksiyete üzerindeki etkileri henüz yeterince incelenmemiştir. Çalışma, Karatay Üniversitesi Etik Kurulu onayı ile Konya Şehir Hastanesi'nde, Ağustos-Aralık 2023 tarihleri arasında gerçekleştirildi. Çalışmaya, genel anestezi uygulanacak 12-18 yaş arası 150 hasta dahil edildi. Preoperatif anksiyete "Spielberger Durumluk Kaygı Ölçeği" (STAI-1) ile, internet bağımlılığı "Young İnternet Bağımlılığı Ölçeği" (İAS) ile ölçüldü. İstatistiksel analizler SPSS ile yapıldı ve Pearson korelasyon, ANOVA ve regresyon analizleri kullanıldı. Hastaların %45.3'ü internet bağımlısıydı ve bu grupta preoperatif anksiyete düzeylerinin daha yüksek olduğu ($r=0.728$, $p<0.01$),ikili karşılaştırmalarda tüm gruplar arasında istaistiksel anlamlı fark olduğu tespit edildi. İnternet bağımlılığı ve preoperatif anksiyete arasında pozitif güçlü bir ilişki bulundu. Ayrıca, yaş ve internete erişim kolaylığının da anksiyete düzeyini artırdığı ve i nternete kolay erişimi olan bireylerde, sınırlı erişimi olanlara kıyasla daha yüksek anksiyete seviyeleri olduğu görülmüştür ($\beta=0.189$, $p=0.018$). İnternet bağımlılığı, cerrahi geçirecek ergenlerde preoperatif anksiyete düzeyini artıran önemli bir faktördür. Yaş ve internete erişim kolaylığı da anksiyete düzeyini etkileyen diğer değişkenlerdir. Bu bulgular, internet bağımlılığının preoperatif süreçlerde göz önünde bulundurulması gerektiğini göstermektedir.
Anahtar Kelimeler: Preoperatif anksiyete, İnternet Bağımlılığı, Ergenlik, Genel anestezik

Ethics Committee Approval: This study was designed and conducted in accordance with the ethical guidelines set forth in the Declaration of Helsinki, and the study protocol was approved by the Karatay University Noninterventional Clinical Research Ethical Committee (Decision no: 2023/005, Date: 02/05/2023)

Informed Consent: This study did not require informed consent.

Authorship Contributions: 1. Conception - 2. Design - 3. Supervision - 4. Fundings - 5. Materials - 6. Data Collection and/or Processing - 7. Analysis and/or Interpretation - 8. Literature Review - 9. Writing - 10. Critical Review

Nuran AKINCI EKİNCİ:1, 2, 3, 4, 5, 6, 7, 8, 9, Mehmet Akif YAZAR:1, 2, 3, 7, 10, Aydın MERMER: 2, 7, 8,10, Rabia KORKMAZ: 2, 5, 6 .

Copyright Transfer Form: Copyright Transfer Formwas signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Received : 13.11.2024

Accepted : 09.12.2024

Published :30.12.2024

How to cite/ Atıf için: Akıncı Ekinci N, Yazar MA, Mermer A, Korkmaz R, The Effect of Internet Addiction on Preoperative Anxiety in Adolescent, Osmangazi Journal of Medicine, 2025;47(1):85-90

1. Introduction

Anxiety, an unpleasant feeling of discomfort that leads to tension, worry, restlessness, and heightened autonomic activity, is a significant concern in the context of surgery. It is quite common among patients admitted for surgery, with preoperative anxiety related to anesthesia and surgery being a prevalent issue (1, 2, 3). This not only affects the mental state but can also lead to autonomic dysfunction, increased inflammatory response, decreased platelet activity, and postoperative pain, thereby negatively impacting both mortality and morbidity (1, 4, 5, 6, 7, 8). Patients experiencing high levels of anxiety require more anesthetic induction agents, and their postoperative recovery process is adversely affected (9, 10, 11).

In the last twenty years, the internet has been an essential aspect of life worldwide, significantly transforming critical areas like communication, information access, sharing, entertainment, and gaming (12, 13, 14). Notably, individuals born after 1995, Generation Z, have learned and internalized internet use at an early age (13, 15). However, uncontrolled internet use is defined as "internet addiction," and this addiction has detrimental effects on mental health, especially among adolescents (15, 16, 17). Adolescents, due to issues in social relationships, introversion, impulsivity, and communication problems, tend to turn to internet use, making them the most vulnerable group to screen addiction. The literature has explored relationships between screen and internet addiction and various mental health issues such as loneliness, anxiety, sleep disorders, depression, and suicidal tendencies (17, 18, 19, 20). However, it is clear that internet addiction among adolescents has a direct impact on their preoperative anxiety levels. In the study, we aimed to evaluate how internet addiction influences preoperative anxiety in adolescents preparing for surgery.

Our secondary goal was to determine if preoperative anxiety varies according to demographic factors. "Patients aged 12 to 18 y/o, scheduled for surgery with general anesthesia, had the psychical status of I-III under ASA (American Society of Anesthesiologists) physical status of I-III and had obtained informed consent from their parents."

2. Materials and Methods

This study was executed at Konya City Hospital between August 2023 and December 2023, with the approval of the Karatay University Faculty of Medicine Ethics Committee (decision dated 02/05/2023, No. 2023/005). The study included 150 patients aged 12-18 who were scheduled for surgery under general anesthesia and classified in physical status of I-III vy ASA, had received consent from their parents.

2.1. Patient Selection

Inclusion criteria required the participants to be between the ages of 12 - 18 with an ASA I-III in addition to voluntary participation in the study. Exclusion criteria included patients who are younger than 12 or older than 18, those with an ASA status of IV or higher, cases requiring emergency surgery, patients scheduled for cardiac surgery, those with a history of psychiatric or mental illness, those using sedative or anxiolytic medications, and patients who were illiterate or did not speak Turkish.

2.2. Study Design

Before the study, all patients were informed about the general anesthesia they would undergo, and detailed explanations were provided. Demographic data were collected from patients who agreed to participate and recorded using a Sociodemographic Data Form. Preoperative anxiety levels were evaluated via the Spielberger State-Trait Anxiety Inventory (STAI FORM TX-1), and internet addiction was evaluated using the Young Internet Addiction Scale (IAS). The questionnaires were distributed to the patients, who were asked to complete them. The questionnaire was considered invalid if more than three questions were answered. Scoring was done manually, and patients' STAI and IAS scores were recorded in SPSS software. To maintain objectivity, the researcher who administered the questionnaire differed from the one who entered the data.

2.3. Measurements

The assessment of internet addiction was carried out through the Young Internet Addiction Scale, consisting of 20 questions, each of which is measured using a 5-point Likert scale (1 = Never, 5 = Always) with the highest possible score being 100. STAI FORM TX-1 is used to measure individuals' anxiety levels at a particular moment and consists of 20 items. The responses provided are rated on a 4-point Likert scale (1 = Not at all, 4 = Completely) with the total score ranging between 20 to 80, which

is interpreted as the higher scores corresponding to higher anxiety levels.

2.4. Statistical Analysis

In order to calculate the sample size, a Type I error rate (α) of 0.05 and statistical power (1-β) of 0.95 were selected to identify the minimum number of participants needed for correlation analyses. The power analysis indicated a minimum sample size of 134 was necessary to detect a moderate effect. To account for potential data loss, the study included 150 patients.

Statistical analyses were carried out via the utilization of SPSS, version 22. The calculations included the mean and the standard deviation for the mean and standard for continuous variables and frequency and percentage values for categorical variables. Data normality was assessed through skewness, kurtosis values, and Z-scores, and differences between groups were analysed using One-way ANOVA.

To assess the main objective, Pearson correlation analysis was applied to calculate how internet addiction affects preoperative anxiety. This analysis was carried out to evaluate the linear relationship and strength between the IAS and preoperative anxiety levels (STAI-1). The Pearson correlation coefficient (r) was utilized to understand whether the two variables exhibited a positive or negative correlation, and determine its statistical significance. For the secondary objective, hierarchical linear regression analysis was conducted to observe whether preoperative anxiety varied according to demographic factors (e.g., age, gender, education level). This approach was selected to assess how much each demographic variable affected preoperative anxiety levels. The independent variables' effects on preoperative anxiety were identified using the regression model.

3. Results

The number of patients registered with the study was 150. The gender distribution was as follows: 57 (38%) were female and 93 (62%) were male. The sample ranged between ages 12 to 18 years with a mean age of 14.98 ±2.1 years. Thirty percent of the patients had undergone previous surgery. Descriptive demographic characteristics are illustrated in Table 1.

Table 1. Demography of the Participants

Characteristics		N	%
Gender	Female	57	%38,0
	Male	93	%62,0
Aged		14,8 ±2,1	
Smoking	Yes	33	%22,0
	No	117	%78,0
ASA*	I	104	%69,3
	II	44	%29,3
	III	2	%1,3
Performed Surgery	Pilonidal sinüs	28	%18,7
	Orthopedics	46	%30,7
	ENT	27	%18,0
	Plastic Surgery	1	%0,7
	Urology	18	%12,0
	Ophthalmology	13	%8,7
	Diğer	17	%11,3
History of Previous Surgery	Yes	45	%30
	No	105	%70
Internet Access	Easy	20	%13.3
	Moderate	61	%40,7
	Difficult	69	%46,0
STAI**	Low	38	25,3%
	Moderate	44	29,3%
	High	68	45,3%

*Data are shown as mean, ±SD, N (%). *ASA: American Society of Anesthesiologists Classification, **STAI-1: State-Trait Anxiety Inventory.*

It was observed that the skewness and kurtosis values of the STAI-I and scores were within the range of ±1.5, and the Z-scores were below ±3.29, indicating a normal distribution.

3.1. Preoperative Anxiety Levels by Internet Usage Levels

Participants' levels of internet addiction were assessed using the Young Internet Addiction Scale (IAS). The mean STAI-1 score for the average internet user group was 34.30 ±7.87, 39.90 ±6.21 for the at-risk internet users, and 49.57 ±7.08 for the internet addicts. These data are detailed in Table 2.

Table 2. Comparison of Internet Addiction Level and STAI-1 Scores

Group	N	Mean	Standard Deviation (SD)	95% Confidence Interval	*P*-value
Average user	20	34,30	7,875	30,61- 37,99	
Risky user	61	39,90	6,209	38,31-41,49	
Dependent user	69	49,57	7,087	47,86-51,27	<0,001

Post-hoc analysis of pairwise comparisons revealed significant differences between average and at-risk users, average and addicted users, and between at-risk and addicted users, with p-values of <0.006, <0.001, and <0.001, respectively.

The fundamental purpose of the study was to examine the relationship between preoperative anxiety and one's internet dependency. Pearson correlation analysis signified a strong positive link between Young IAS score and preoperative anxiety (STAI-1 score) ($r = 0.728$, $p < 0.01$). This result demonstrates that as internet addiction increases, so does the level of preoperative anxiety.

Our subsidiary aim was to assess whether preoperative anxiety varied based on demographic factors. Hierarchical linear regression analyses were conducted in two stages for this purpose. In the first stage, only the internet addiction score was included as an independent variable. At this stage, the internet addiction score was found to significantly predict preoperative anxiety levels ($\beta = 0.715$, $p < 0.001$). In the second stage, demographic variables were included in the model. At this stage, the effect of the internet addiction score on preoperative anxiety persisted ($\beta = 0.511$, $p < 0.001$). In addition, age ($\beta = 0.184$, $p = 0.008$) and internet access status ($\beta = 0.189$, $p = 0.018$) also had significant effects on preoperative anxiety. Moreover, Variance Inflation Factor (VIF) values were checked in the multiple linear regression analysis to assess multicollinearity, and no multicollinearity was found.

After controlling for demographic variables, the effect of the internet addiction score on the STAI score decreased from 0.715 to 0.495, though the effect remained significant. The internet addiction score significantly accounted for 13.7% of the total variance in the STAI score. According to the regression model controlling for demographic variables, a 1-unit increase in the internet addiction score significantly predicted a 0.277-unit increase in the STAI score. Similarly, a 1-unit elavate in the age variable predicted a 0.783-unit increase in the STAI score.

4. Discussion

Following the study measuring the impact of internet addiction on preoperative anxiety in patients aged 12-18 years undergoing general anesthesia, we discovered a robust positive correlation between the two with the rate of preoperative anxiety in the internet-addicted group being 49.57%.

In the digital age, there has been major attention drawn to concerns around the younger generation's addiction to the internet, with major links being made between internet usage and a variety of psychological issues such as sleep deprivation, depression, isolation and anxiety. Many studies in related literature confirm that addiction to internet affects the psychological health of adolescents, negatively. For example, studies by Tuncay and Üstündağ have observed a positive link associating higher internet usage with poor sleep quality, depression, and general anxiety in adolescents (19, 21). A study by Tsitsika et al. found that adolescents with internet addiction were 3.8 times more vulnerable to psychiatric ailments compared to healthy individuals (22). Studies like those by Dalbudak and Şimşek have also reported that internet addiction in adolescents increases psychiatric issues, manifesting in symptoms such as anxiety, attention deficit, and depression (17, 18). Our findings confirmed a strong positive link between internet addiction and preoperative anxiety

(r = 0.728), which is consistent with the findings of previous studies.

Various demographic factors influencing preoperative anxiety levels play an essential role in managing surgical processes. It has been observed that preoperative anxiety levels increase with age. This finding aligns with the literature, such as studies by Taşdemir and Peker, which reported that concerns about surgical processes increase with age and that age is a factor that heightens anxiety (23, 24). In the study, age was found to significantly increase one's vulnerability to preoperative anxiety following excessive internet usage.

In addition, internet access status also had a notable impact on anxiety. Individuals with constant internet access were monitored to suffer from higher levels of preoperative anxiety compared to those with limited access. This result aligns with findings in the literature that explore the connection between internet addiction and psychosocial issues. For example, studies by Şimşek and Younes have shown that internet access and usage increase anxiety and stress levels (18, 25). Particularly among young individuals, constant access to the internet can create psychological pressure and stress, leading to heightened anxiety in the preoperative period.

Some studies have reported that the sex of a participant has a more profound effect on their tendency towards developing preoperative anxiety (26), but our study found no such impact. This difference may stem from our study's focus on the adolescent population. In adolescents, social and environmental conditions are known to be more influential than gender differences.

Despite precautions being taken, the study was still inhibited by several limitations. Firstly, since our study exclusively focused on 12-18 year olds, the results may not apply to adults or elderly populations, suggesting that the connection between internet addiction and preoperative anxiety may manifest differently in other age groups. Secondly, the data collection methods in the study were based on the method of self-reporting. STAI and Young IAS score were completed based on participants' self-reports. Such scales may be subject to bias stemming from social desirability or may not fully capture participants' conditions. Using more objective measures to assess psychological variables like anxiety and internet addiction could enhance the reliability of the results. Lastly, the cross-sectional model of the study renders it impossible to determine causal links; the temporal course of the effects of internet addiction can only be examined through a longitudinal study that follows participants over the course of many years.

In conclusion, this research observed that as internet addiction increased, preoperative anxiety levels also rose. Demographic factors such as one's age and ease of internet access were also observed to significantly impact anxiety levels. However, future research on larger populations with different demographic features will help bring us closer to a more comprehensive understanding of the topic surrounding internet addiction and the effect that it has on increasing the rates of preoperative anxiety.

REFERENCES

1. Friedrich S, Reis S, Meybohm P, Kranke P. Preoperative anxiety. Curr Opin Anesthesiol. 2022;35(6):674-8.
2. Zemła A, Nowicka-Sauer K, Jarmoszewicz K, Wera K, Batkiewicz S, Pietrzykowska M. Measures of preoperative anxiety. Anestezjol Intens Ter. 2019;51(1).
3. Tulloch I, Rubin JS. Assessment and management of preoperative anxiety. J Voice. 2019;33(5):691-6.
4. Stamenkovic DM, Rancic NK, Latas MB, Neskovic V, Rondovic GM, Wu JD, et al. Preoperative anxiety and implications on postoperative recovery: what can we do to change our history. Minerva Anestesiol. 2018;84(11):1307-17.
5. Von Känel R, Rosselet K, Gessler K, Haeussler A, Aschmann J, Rodriguez H, et al. Preoperative depression and anxiety as predictors of postoperative C-reactive protein levels in patients undergoing cardiac surgery: a prospective observational study. Swiss Med Wkly. 2022;152:40018.
6. Wu H, Huang Y, Tian X, Zhang Z, Zhang Y, Mao Y, et al. Preoperative anxiety-induced glucocorticoid signaling reduces GABAergic markers in spinal cord and promotes postoperative hyperalgesia by affecting neuronal PAS domain protein 4. Mol Pain. 2019;15:1744806919850383.
7. Bayrak A, Sagiroglu G, Copuroglu E. Effects of preoperative anxiety on intraoperative hemodynamics and postoperative pain. J Coll Physicians Surg Pak. 2019;29(9):868-73.
8. Gao Q, Mok HP, Zhang HY, Qiu HL, Liu J, Chen ZR, et al. Inflammatory indicator levels in patients undergoing aortic valve replacement via median sternotomy with

preoperative anxiety and postoperative complications: a prospective cohort study. J Int Med Res. 2021;49(2):0300060520977417.
9. Chen YYK, Soens MA, Kovacheva VP. Less stress, better success: a scoping review on the effects of anxiety on anesthetic and analgesic consumption. J Anesth. 2022;36(4):532-53.
10. Baagil H, Baagil H, Gerbershagen MU. Preoperative Anxiety Impact on Anesthetic and Analgesic Use. Medicina. 2023;59(12):2069.
11. Rodrigues HF, Furuya RK, Dantas RAS, Rodrigues AJ, Dessotte CAM. Association of preoperative anxiety and depression symptoms with postoperative complications of cardiac surgeries. Rev Lat Am Enfermagem. 2018;26:e3107.
12. Lozano-Blasco R, Latorre-Martínez M, Cortés-Pascual A. Screen addicts: A meta-analysis of internet addiction in adolescence. Child Youth Serv Rev. 2022;135:106373.
13. Singh R. Perils of screen addiction. AKGEC Int J Technol. 2022;13(1):40-4.
14. Bülbül H, Tunç T. Phone and game addiction: scale analysis, the starting age and its relationship with academic success. Vizyoner Derg. 2018;9(21):1-13.
22. Psychological Needs. Bağımlılık Derg. 2022;23(1):8-21.
23. Tsitsika A, Critselis E, Louizou A. Determinants of Internet addiction among adolescents: a case-control study. Sci World J. 2011;11:866-74.
24. Taşdemir A, Erakgün A, Deniz MN, Çertuğ A., Comparison of Preoperative and Postoperative Anxiety Levels with State-Trait Anxiety Inventory Test in Preoperatively Informed Patients. Turk J Anesth Reanim. 2013;41(2).
25. Peker K. Comparison of Beck and State-Trait Anxiety Inventories in the Assessment of Preoperative Anxiety. J Anesth Resusc Sci. 2020;28(2).
26. Younes F, Halawi G, Jabbour H, El Osta N, Karam L, Hajj A, et al. Internet addiction and relationships with insomnia, anxiety, depression, stress and self-esteem in university students: a cross-sectional designed study. PLoS One. 2016;11(9):e0161126.
27. Yen JY, Ko CH, Yen CF, Wu HY, Yang MJ. The comorbid psychiatric symptoms of Internet addiction: attention deficit and hyperactivity disorder (ADHD), depression, social phobia, and hostility. J Adolesc Health. 2007;41:93-8.
15. Daysal B, Yılmazel G. Smartphone addiction and adolescence via public health view. Turk J Fam Med Prim Care. 2020;14(2):316-22.
16. Bickham DS. Current research and viewpoints on internet addiction in adolescents. Curr Pediatr Rep. 2021;9:1-10.
17. Dalbudak E, Evren C. The relationship of Internet addiction severity with Attention Deficit Hyperactivity Disorder symptoms in Turkish University students; impact of personality traits, depression and anxiety. Compr Psychiatry. 2014;55(3):497-503.
18. Şimşek N, Akça NK, Şimşek M. Internet addiction and hopelessness in high school students.TAF Prev Med Bull. 2015;14(1):7-14.
19. Koças F, Şaşmaz T. Internet addiction increases poor sleep quality among high school students. Turk J Public Health. 2018;16:167-77.
20. Kahraman Ö, Demirci EÖ. Internet addiction and attention-deficit–hyperactivity disorder: Effects of anxiety, depression and self-esteem. Pediatr Int. 2018;60(6):529-34.
21. Üstündağ A., The Relationship Between Adolescents' Instagram Addiction Levels and

Osmangazi Journal of Med, 2025;47(1): 91-94
DOI: 10.20515/otd.1549070

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Effect of Closing Processus Vaginalis in Orchidopexy to Recurrence and Testicular Atrophy – 15 Years Experience

Orşidopekside Patent Processus Vajinalis Kapatılmasının Nüks ve Atrofi üzerine Etkisi-15 Yıllık Deneyim

[1]Nilsun Kuas, [2]Ufuk Ateş, [2]Ergun Ergün, [2]Aysel Mammadlı, [3]İrem Semiha Köksaldı , [4]Atike Atasoy , [2]Gülnur Göllü Bahadır, [2]Meltem Bingöl Koloğlu, [2]Emin Aydın Yağmurlu , [2]Ahmet Murat Çakmak

[1]Department of Pediatric Surgery, Division of Pediatric Urology, Van Training and Research Hospital, Van, Türkiye
[2]Department of Pediatric Surgery, Ankara University, Faculty of Medicine, Ankara, Türkiye
[3]Plastic Reconstructive and Aesthetic Surgery at Firat University Medical Faculty Hospital, Elazığ, Türkiye
[4]Pediatric Surgery Specialist, Sincan Education and Research Hospital, Ankara, Türkiye

ORCID ID of the authors
NK. 0000-0001-6951-3494
UA. 0000-0001-6591-7168
EE. 0000-0001-8806-4022
AM. 0009-0008-6531-1279
İSK. 0000-0002-4786-2981
AA. 0000-0002-8267-197X
GGH. 0000-0001-8163-2226
MBK. 0000-0001-7726-7633
AY. 0000-0002-3294-4482
AMÇ. 0000-0002-4870-8361

Correspondence / Sorumlu yazar:
Ufuk ATEŞ

Department of Pediatric Surgery, Ankara University, Faculty of Medicine, Ankara,Türkiye

e-mail: drufukates@gmail.com

Abstract: Undescended testis is one of the most common pathologies encountered by pediatric surgeons. In traditional orchidopexy operation, patent processus vaginalis (PPV) is dissected from testicular vessels and spermatic cord. In this study, it was aimed to compare the results of undescended testis patients with and without PPV closure in terms of recurrence and atrophy. After the approval of the local ethics committee, patients who were operated for undescended testis between January 2007 and December 2022 were evaluated. Patients were determined in two groups. first group was with PPV ligation (n=171), second group was without PPV ligation (n=1637). Inguinal hernia was not observed after any operation. There were 23 recurrences (%13,4) in group 1 and 48 recurrences (%2,9) in group 2. According to the preoperative evaluation; A decrease in testicular size was detected in 5 patients (2.9%) in Group 1 and 8 patients (0.4%) in Group 2 in the postoperative follow-up. There is no need to ligate the PPV with additional dissection and open the external oblique fascia if it is predicted that the spermatic cord and testicular vessels may come to scrotum without tension in patients who underwent orchiopexy surgery.
Keywords: Undescended Testis, Orchidopexy, Processus Vajinalis

Özet: İnmemiş testis, çocuk cerrahlarının en sık karşılaştığı patolojilerden biridir. Geleneksel orşiyopeksi operasyonunda, açık prosessus vajinalis (PPV), testis damarları ve spermatik korddan diseke edilir. Bu çalışmada, PPV kapatılması olan ve olmayan inmemiş testis hastalarının sonuçlarının nüks ve atrofi açısından karşılaştırılması amaçlandı. Yerel etik kurul onayı alındıktan sonra Ocak 2007 - Aralık 2022 tarihleri arasında inmemiş testis nedeniyle opere edilen hastalar değerlendirildi. Hastalar iki gruba ayrıldı. Birinci grupta PPV ligasyonu olan (n=171), ikinci grupta PPV ligasyonu olmayan (n=1637) hastalar olmak üzere toplam 2 grup oluşturuldu. Operasyonlardan sonra takipte inguinal herni izlenmedi. Grup 1'de 23 nüks (%13,4), grup 2'de ise 48 nüks (%2,9) görüldü. Ameliyat öncesi değerlendirme ile karşılaştırıldığında; ameliyat sonrası takipte Grup 1'de 5 hastada (%2,9) ve Grup 2'de 8 hastada (%0,4) testis boyutunda azalma tespit edildi. Orşiopeksi ameliyatı geçiren hastalarda spermatik kord ve testis damarlarının gerginlik olmadan skrotuma gelebileceği öngörülüyorsa PPV' yi ek disseksiyonla bağlamaya ve eksternal oblik fasyayı açmaya gerek yoktur.
Anahtar Kelimeler: İnmemiş Testis, Orşiopeksi, Processus Vajinalis

Ethics Committee Approval: This study was designed and conducted in accordance with the ethical guidelines set forth in the Declaration of Helsinki, and the study protocol was approved by the Ankara University Clinical Research Ethical Committee (Decision no: İ11-693-22 Date: 10.01.2023)

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis

Authorship Contributions: All authors contributed equally to the study.

Copyright Transfer Form: Copyright Transfer Formwas signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Received : 22.09.2024

Accepted : 12.12.2024

Published : 17.12.2024

How to cite/ Atıf için: Kuas N, Ateş U, Ergün E, Mammadlı A, Köksaldı İS , Atasoy A , Göllü Bahadır G, Bingöl Koloğlu M, Yağmurlu EA, Çakmak AM, Effect of Closing Processus Vagınalis in Orchıdopexy to Recurrence and Testicular Atrophy – 15 Years Experience, Osmangazi Journal of Medicine, 2025;47(1):91-94

1. Introduction

Undescended testis is one of the most common pathologies encountered by pediatric surgeons, with a rate of 9% in term births and 30% in preterm births. [1]. The incidence of the condition at 1 year of age is 0.8% [2]. More than 90% of patients are thought to have patent processus vaginalis (PPV). [1]. It is recommended that uncircumcised testes be operated on between 6 months and 1 year to prevent malignancy and infertility [1].

The PPV has been found to be open in 80-94% of neonates and 20% of adults, and the timing of PPV closure is still unknown [3]. In traditional orchidopexy surgery, the PPV is dissected from the testicular vessels and spermatic cord, and after dissection PPV is closed with a stitch. [4, 5]. However, this procedure may cause damage to the vessels and atrophy due to the damaged vessels [6, 7].

The aim of this study was to compare the outcomes of patients with undescended testis with and without PPV closure in terms of recurrence and atrophy.

2. Materials and Methods

After approval by the local ethics committee, patients who had undergone surgery for undescended testis between January 2007 and December 2022 were evaluated. Patient demographic and clinical findings were obtained from the hospital record system. Patients who underwent laparoscopic orchidopexy, had sex differentiation disorder, and were found to have an inguinal hernia on preoperative examination were excluded from the study. All patients underwent surgery via a traditional inguinal approach. Postoperative follow-up of the testis, which was smaller before surgery due to age and/or compared with the contralateral testis, followed by comparison with preoperative assessment and comparison with the contralateral testis. Patients were divided into two groups. The first group was with PPV ligation, and the second group was without PPV ligation.

Table 1. Inguinal canal opening and PPV closure rates

	Need to open inguinal canal(External oblique's fascia)	No need to open inguinal canal (External oblique's fascia)	Total
Group 1 (With PPV Closure)	n=68	n=103	n=171
Group 2 (Without PPV Closure)	n=27	n=1610	n=1637

Surgical technique: after the fibrotic adhesions were released, it was checked at each stage whether the testicles descended into the scrotum. If sufficient length was achieved, a Dartos pouch was created and the testis was placed in the scrotum. If sufficient length was not obtained and the PVV structure was detected, it was dissected and ligated. If sufficient length was again not obtained, the inguinal canal was opened and dissection continued. If sufficient length was not obtained after opening the inguinal canal, the PPV structure was dissected and ligated.

Statistical Package for Social Sciences (SPSS, version 15.0, Chicago, IL.) was used to perform the analyses. In descriptive statistics, quantitative variables were expressed as mean ± standard deviation or median (minimum-maximum) according to normal distribution, and qualitative variables were expressed as frequency (percent). The demographic and clinical data of the subjects included in the study were analysed with Pearson chi-square or Fisher's exact test for qualitative variables. The accepted statistical significance level was $p < 0.05$.

3. Results

The mean age at surgery was 37 months (minimum 6-maximum 119). A total of 1808 testicles underwent orchidopexy. Of these, 171 testes were in group 1 and 1637 testes were in group 2. The details of the surgery are shown in Table 1. At preoperative examination, 1775 testes were found in the inguinal canal and 33 testes were brought to the inguinal canal. It was observed that the undescended testes ligated with PPV were higher and more tense during surgery, so the PPV was ligated to reduce the tension and allow stretching of the testis.

No inguinal hernia was observed after surgery during the follow-up period. There were 23 recurrences (13.4%) in group 1 and 48 recurrences (2.9%) in group 2. The recurrence rate in group 1 was statistically higher ($p < 0.001$).

In group 1, 56 patients (32.7%) had testicles that were too small before surgery. At postoperative follow-up, the finding was found to persist in 6 patients (3.5%). A reduction in testicular size was noted in 5 patients (2.9%) compared to the preoperative assessment. In group 2, 215 patients (13.1%) had testes that were too small before surgery. At postoperative follow-up, the finding was found to persist in 76 patients (4.6%). A reduction in testicular size was noted in 8 patients (0.4%) compared to the preoperative assessment.

The testicular dimensions were determined by physical examination. The expected size according to age and contralateral testes, the patient's previous and subsequent examination findings were compared.

Infection of the surgical site was noted in 3 patients and hematoma in 1 patient. No further complications occurred after surgery.

4. Discussion and Conclusion

The incidence of undescended testis at about 1 year of age is 0.8% [2]. The testis is palpable in 80% of patients and 90% of palpable testes are located in the inguinal canal [1]. Patients with undescended testis have a higher risk of infertility, malignancy, and testicular torsion compared with the general population; therefore, it is recommended that these patients undergo surgery before 18 months of age [1, 3].

PPV is a peritoneal appendage associated with testicular descent [8]. Non-obliterated PPV is related to undescended testis, hydrocele and inguinal hernia [9]. It is believed that 90% of patients with undescended testis have concomitant PPV [1].

It is recommended to ligate the PPV after dissection of spermatic cord and vessels in traditional orchidopexy [3]. Davey et al. have shown that dissection of the PPV results in 60% greater expansion of the spermatic cord and vessels [10]. It is believed that the main causes of failed orchidopexy are inadequate expansion of the spermatic cord, open PPV, and inadequate fixation of the scrotum [11]. However, in this study, recurrence rates were found to be statistically higher in the closed PPV group.

The patency rate of the processus during orchiopexy was 36.1% as reported by Dayanc et al [12]. More importantly, they were able to successfully perform orchiopexy in 94.4% of cases and found no hernia or hydrocele formation at follow-up [13]. Iyer et al. reported a success rate of 96.2% in 367 orchiopexies performed with the high scrotal approach [14]. This study found that the recurrence rate was lower in patients whose PPV was not closed.

Some studies recommend not closing the PPV after dissection, but other studies recommend closing the PPV because it may lead to inguinal hernia [15]. In this study, inguinal hernia was not observed in any of the patients. Ceccanti et al. and Jain et al. showed similar results to our study [4, 6], in which no inguinal hernia occurred after orchidopexy.

Schier et al. stated that in laparoscopic hernia repair there is no difference between cutting the hernia sac and ligating it, explaining that the open inner ring of the inguinal canal does not clinically cause hernia [16]. Handa et al, on the other hand, argued that closure of the inner ring of the inguinal canal is unnecessary in laparoscopic orchipexia and does not clinically cause inguinal hernia [17].

Since the PPV is adjacent, care must be taken not to injure the vas deferens and vessels during dissection [18]. Testicular atrophy, which may occur after orchiopexy, may lead to serious loss of testicular function in the future. The incidence of testicular atrophy associated with orchiopexy ranges from 8-32% [19]. Dissection of the PPV can lead to damage of the spermatic cord and testicular vessels [15]. It is more risky at young age [6, 7]. In this study, the testes were better after surgery in both groups. Shirazi et al. compared two groups of undescended testes [15]. In the first group, the PPV was closed, and in the second group, the PPV was stretched. The atrophy rate was statistically lower in the second group. Damage to the vessels during dissection or suturing of the PPV may lead to atrophy.

The exact closure time of the PPV is unknown. It has been found to be open in 80-94% of neonates, while it is open in 20% of adults [3]. In previous studies, the detection rate of PPV was determined to be 20-59% in scrotal orchiopexies and 90% in laparoscopic orchiopexies, and it reaches up to 100% in laparoscopy-assisted transscrotal orchiopexies [8]. The inconsistencies in the

detection of PPV can be explained not only by the differences between incisions and approaches, but also by the incomplete understanding of its etiology and closing process. We believe that PPV dissection is unnecessary for testes that can be easily lowered into the scrotum.

In this study, no increase in complications related to recurrence and herniation was observed when the PPV was not fixed in the testis but an extension of the cord was achieved by dissection, which would easily reach the scrotum. Because PPV dissection and ligation procedures may cause damage to the spermatic cord and vascular structures in the testis in patients and may cause infertility and testicular atrophy in the future, we believe that dissection should be avoided.

The study has limitations. One of the limitations is that the study presented was a retrospective evaluation, so the groups were not randomly divided and the number of patients in the groups was unevenly distributed. Another limitation is that the decision to perform PPV ligation was based on the tension of the testicular structures during surgery. To obtain more accurate and reliable results, it is necessary to perform a randomized, controlled, and prospective study.

There is no need to ligate the PPV with additional dissection and to open the fascia obliqua externa if it can be assumed that the spermatic cord and testicular vessels can reach the scrotum without tension in patients who have undergone orchiopexy for undescended testis. There is no difference in recurrence and iatrogenic inguinal hernias in operations performed without dissection and ligation. Additional dissections lead to a higher risk of infertility and testicular atrophy in the future.

REFERENCES

1. Elseth A, Hatley RM. Orchiopexy. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560904/
2. Alchoikani N, Ashour K. Ascending testis: A congenital predetermined condition. J Pediatr Urol. 2021 Apr;17(2):192.e1-192.e3.
3. Radmayr C., Bogaert G., Burgu B., et al. Management of undescended testes. In: EAU Guidlines on Paediatric Urology. 2022. Available at: https://uroweb.org/guidelines/paediatric-urology Accessed on 15 May 2023.
4. Ceccanti S, Zani A, Mele E, Cozzi DA. Orchidopexy without ligation of the processus vaginalis is not associated with an increased risk of inguinal hernia. Hernia. 2014 Jun;18(3):339-42.
5. Thorup J, Haugen S, Kollin C, et al. Surgical treatment of undescended testes. Acta Paediatr. 2007;96(5):631-637.
6. Jain VK, Singh S, Garge S, Joshi M, Sanghvi J. Orchidopexy san ligation technique of orchidopexy. Afr J Paediatr Surg. 2011;8(1):112-114.
7. Tabrizian F, Raisolsadat SM, Houshmand B, Yaghubi MA. Assessment of the necessity of sac high ligation in inguinal hernia open surgery among children. J Pediatr Surg. 2013;48(3):547-549.
8. Zhao W, Su C, Li S, Mo Z. Comparison of the Detection and Ligation of Patent Processus Vaginalis Between Laparoscopy-Assisted Transscrotal Orchiopexy and Single Scrotal Incision Orchiopexy. Front Surg. 2022;8:819057. Published 2022 Jan 31.
9. Tanyel, F.C., Obliteration of processus vaginalis: aberrations in the regulatory mechanism result in an inguinal hernia, hydrocele or undescended testis. Turk J Pediatr, 2004. 46 Suppl: p. 18-27 PMID:15499794
10. Davey RB. Orchidopexy: the relative importance of each step of mobilisation. Pediatr Surg Int. 1997;12(2/3):163-164 PMID:9069223
11. Noseworthy J. Recurrent undescended testes. Semin Pediatr Surg. 2003;12(2):90-93.
12. Dayanç M, Kibar Y, Tahmaz L, Yildirim I, Peker AF. Scrotal incision orchiopexy for undescended testis. Urology. 2004;64(6):1216-1219.
13. Bassel YS, Scherz HC, Kirsch AJ. Scrotal incision orchiopexy for undescended testes with or without a patent processus vaginalis. J Urol. 2007;177(4):1516-1518.
14. Iyer, K.R., Kumar, V., Huddart, S.N., Bianchi A. The scrotal approach. Pediatr Surg Int 10, 58–60 (1995).
15. Shirazi M, Safavi S, Makarem A, Malekmakan L. Comparison Between Processus Vaginalis Sac Tightening Technique and the Conventional Technique in Orchiopexy Surgery Over 10 Years. Res Rep Urol. 2020;12:129-136. Published 2020 Mar 18.
16. Schier F. Laparoscopic inguinal hernia repair-a prospective personal series of 542 children. J Pediatr Surg. 2006;41(6):1081-1084.
17. Handa R, Kale R, Harjai MM. Laparoscopic orchiopexy: is closure of the internal ring necessary?. J Postgrad Med. 2005;51(4):266-268 PMID:16388167
18. Lin J, Li D, Chen J, Lin L, Xu Y. Inguinal hernia repair by Bianchi incision in boys: a retrospective study. Pediatr Surg Int. 2018;34(3):289-295.
19. Ok F, Durmus E, Ayaz M. The role of the resistive index in predicting testicular atrophy after orchiopexy in unilateral undescended testis. Pediatr Surg Int. 2022;39(1):38. Published 2022 Dec 8.

Osmangazi Journal of Med, 2025;47(1): 95-101
DOI: 10.20515/otd.1578873

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Evaluation of Psychological Symptoms and Quality of Life in Patients with Early-Stage Mycosis Fungoides: A Case-Control Study

Erken Evre Mikozis Fungoides Hastalarında Psikolojik Belirtiler ve Yaşam Kalitesinin Değerlendirilmesi: Bir Vaka-Kontrol Çalışması

[1]Esra Ağaoğlu, [2] Hanife Merve Akça, [1]Niyazi Kürşat Çayır, [1]Hilal Kaya Erdoğan, [1]Ersoy Acer

[1]Eskisehir Osmangazi University Faculty of Medicine, Department of Dermatology, Eskisehir, Türkiye
[2]Karamanoğlu Mehmetbey University Faculty of Medicine, Department of Dermatology, Karaman, Türkiye

ORCID ID of the authors
EA. 0000-0001-8985-6224
HMA. 0000-0001-8280-7470
NKÇ. 0009-0004-0486-3679
HKE. 0000-0002-8172-1920
EA. 0000-0002-6041-6636

Correspondence / Sorumlu yazar:
Esra AĞAOĞLU

Eskisehir Osmangazi University Faculty of Medicine, Department of Dermatology, Eskisehir, Türkiye

e-mail: esraeagaoglu@gmail.com

Abstract: Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma. This study was designed to measure psychological symptoms and health-related quality of life in patients with early-stage MF and compare the results with controls. Forty patients with early-stage MF and 40 age- and gender-matched healthy controls were included in the study. The sociodemographic characteristics of all participants were recorded and Depression, Anxiety and Stress Scale-21 (DASS-21) was administered to measure depression, anxiety and stress levels. Additionally, Skindex-29 was applied to assess the quality of life in MF patients. No significant difference was detected between patient and control groups of MF regarding DASS-21 subscales scores and the total scores. Both symptom and emotion subscale scores of Skindex-29 were found to be statistically higher in female MF patients. Older MF patients had worse symptoms and functional impairment according to Skindex-29. The DASS-21 total scores were positively correlated with all Skindex-29 subscale scores in MF patients. In conclusion, this study demonstrated that quality of life in early-stage MF may be negatively affected in elderly and female patients. Health-related quality of life was more affected in patients with increased levels of depression, anxiety and stress. The quality of life of MF patients can be increased by improving their psychological health.
Keywords: Mycosis fungoides, depression, anxiety, stress, quality of life

Ethics Committee Approval: This study was approved by the Ethics Committee of the Eskisehir Osmangazi University (Decision no: 51, Date: 03.10.2024).

Informed Consent: The authors declared that informed consent form was signed by the patient.

Authorship Contributions: All authors contributed equally to the study.

Copyright Transfer Form: Copyright Transfer Formwas signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Özet: Mikozis fungoides (MF) en sık görülen kutanöz T hücreli lenfoma türüdür. Bu çalışma erken evre MF hastalarında psikolojik belirtiler ve sağlıkla ilişkili yaşam kalitesini ölçmek ve sonuçları kontrollerle karşılaştırmak amacıyla tasarlanmıştır. Çalışmaya erken evre MF tanılı 40 hasta ve yaş ve cinsiyete uygun 40 sağlıklı kontrol dahil edildi. Tüm katılımcıların sosyodemografik özellikleri kaydedildi ve depresyon, anksiyete ve stres düzeylerini ölçmek için Depresyon, Anksiyete ve Stres Ölçeği-21 (DASÖ-21) uygulandı. Ayrıca, MF hastalarında yaşam kalitesini değerlendirmek için Skindex-29 uygulandı. MF'li hasta ve kontrol grubu arasında DASS-21 alt ölçek puanları ve toplam puanlar açısından anlamlı bir fark saptanmadı. Skindex-29'un semptom ve duygu alt ölçek puanları kadın MF hastalarında istatistiksel olarak daha yüksek bulundu. Skindex-29'a göre ileri yaş MF hastalarının daha kötü semptomları ve işlevsel bozuklukları bulunmaktaydı. DASS-21 ölçeği toplam puanları MF hastalarında tüm Skindex-29 alt ölçek puanlarıyla pozitif korelasyon gösterdi. Sonuç olarak erken evre MF'te yaşam kalitesi ileri yaş ve kadın hastalarda olumsuz olarak etkilenebilmektedir. Depresyon, anksiyete ve stres düzeyleri yüksek hastalarda sağlıkla ilişkili yaşam kalitesinin daha fazla etkilendiği görüldü. MF hastalarının psikolojik sağlıklarının iyileştirilmesiyle yaşam kaliteleri artırılabilir.
Anahtar Kelimeler: Mikozis fungoides, depresyon, anksiyete, stres, yaşam kalitesi

Received : 05.11.2024
Accepted : 30.12.2024
Published : 02.01.2025

How to cite/ Atıf için: Ağaoğlu E, Akça HM, Çayır NK, Kaya Erdoğan H, Acer E, Evaluation of Psychological Symptoms and Quality of Life in Patients with Early-Stage Mycosis Fungoides: A Case-Control Study, Osmangazi Journal of Medicine, 2025;47(1):95-101

1. Introduction

Mycosis fungoides (MF) is a mature primary T-cell lymphoma of the skin. It is characterized by the monoclonal proliferation of CD4+ T cells located in the skin. As the most common form of primary cutaneous lymphomas, MF constitutes approximately 60% of all primary non-Hodgkin lymphoma of the skin (1). MF is generally seen in older patients with median age at diagnosis between 55 and 60 years old and affecting more men than women (1.6–2.0:1). The majority of MF patients are diagnosed with early-stage disease. In the early stage of the disease, skin lesions typically appear as erythematous and atrophic patches located in non-sun-exposed areas of the body, often accompanied by itching with variable concomitant ulceration and alopecia (2, 3).

The staging of the MF is based on the TNMB (tumor-node-metastasis-blood) classification revised by the International Society of Cutaneous Lymphoma (ISCL)/European Organization for Research and Treatment of Cancer (EORTC). According to this classification, stage IA, IB or IIA is considered early-stage MF and most patients are diagnosed at this stage (4). Clinically, MF progresses through four stages: patch, plaque, tumor, and erythroderma. The most important prognostic factors in MF include the patient's age, the type and extent of skin involvement, the stage of the disease, the presence of extracutaneous involvement, and the detection of pathological cells in peripheral blood. Skin-directed therapies including topical corticosteroids, topical retinoids, phototherapy and localized radiotherapy are recommended in the treatment of early-stage MF (2, 3, 5).

Beyond the burden of the disease itself, the chronic, recurrent course of disease significantly impact negatively the patients' quality of life. Even in patients with an early-stage of disease, frequent hospital visits, diagnostic procedures, and the possibility of treatment-related side effects may cause anxiety in patients. Additionally, the psychosocial effects of fatigue and sleep disorders may increase the anxiety level of patients and lead to depressive mood disorders (6-8). Considering the effects of psychosocial health of the disease, in this study we aimed to evaluate the depression, anxiety and stress levels and quality of life in early-stage MF.

2. Materials and Methods

Study Population and Recruitment

We enrolled 40 early-stage MF patients and 40 healthy controls aged between 18-80 years. The study protocol was approved by Eskisehir Osmangazi University Ethics Committee. All individuals signed the informed consent form. We confirmed the diagnoses of all MF patients by histopathologically. Exclusion criteria included the use of psychotropic medication concurrently or within the previous 6 months. Sociodemographic data of the volunteers were recorded. In MF patients, the age of disease onset, duration of disease, presence of concomitant systemic or skin disease, stage of the disease, pathological lymph node involvement and current treatments were recorded by a dermatologist. The control group consisted of those who applied to our outpatient clinic with diagnoses such as melanocytic nevus or verruca vulgaris and hospital staff who did not have any psychodermatological disease.

Questionnaires

We evaluated the participants' status of depression, anxiety and stress with Depression Anxiety Stress Scale-21 (DASS-21) which is developed by Lovibond et al. in 1995 (9). DASS-21 consisted of three subscales each containing seven items scored between 0 and 3. The 21 items of the scale were evaluated on a 4-point Likert Scale (0 = Not at all, 1 = applied to me to some degree or some of the time, 2 = applied to me to a considerable degree or a good part of the time, 3 = applied to me very much or most of the time). The validity and reliability of the Turkish version of the DASS-21 was conducted by Sarıcam (10).

MF patients' quality of life was measured by Skindex-29 which is developed by Chren et al (11). This instrument is a self-administered 29-item questionnaire that explores 3 specific aspects of quality of life: effects of skin disease on functioning, emotions and physical symptoms. The answers of the scale are evaluated by converting them to a linear scale, with the "never" option being "0" and the "always" option being "100". Higher scores indicate a greater effect of skin disease on quality of life. The Turkish version of Skindex-29 was established successfully with validity and reliability (12).

Statistical Analysis

The data analyses were performed with SPSS 21.0 Software Package Program Inc., Chicago. Considering the data numbers in the evaluated groups, the relevant data were examined in terms of compliance with normal distribution using one of the Kolmogorov-Smirnov or Shapiro-Wilk tests. Kruskal Wallis H test and Mann Whitney U test were used for data that did not comply with normal distribution. One-Way ANOVA test was used for data that complied with normal distribution, post-hoc Tukey test and Independent-Samples T test were used for comparisons between groups. Since all data evaluated for correlation did not comply with normal distribution, Spearman correlation analysis was used in all correlation evaluations performed in the study. Chi-square test was used for evaluation of categorical data. In all analyzes, $p<0.05$ was considered statistically significant.

3. Results

Of the MF patients, 21 (52.5%) were male and 19 (47.5%) were female. Of the control group, 20 (50.0%) were male and 20 (50.0%) were female. Mean age was 55.32 ± 13.64 in MF group and was 50.72 ± 12.53 in control group. MF patients and controls were similar by distribution of gender, age and marital status ($p>0.05$). The mean disease duration of MF patients was 11.28 ± 14.67 months (Table-1). Thirty-one (77.5%) of the MF patients were stage IA, 5 (12.5%) were stage IB, and 4 (10.0%) were stage IIA. Fifteen (37.5%) of our patients were receiving topical steroids, 9 (22.5%) were receiving topical steroids and acitretin, 8 (20.0%) were receiving topical steroids and narrow-band ultraviolet B phototherapy, and 3 (7.5%) were receiving topical steroids and topical bexarotene. Reactive lymph node involvement was detected in 3 (7.5%) of the MF patients and none of the patients had pathologic lymph node involvement. There were no significant differences between patient and control groups of DASS-21 subscales scores and the total scores ($p> 0.05$) (Table-2).

Table 1. Characteristics in MF patients and control groups

Characteristics	Patient group	Control group	p
Sex			
Male	21 (52.5%)	20 (50.0%)	0.823
Female	19 (47.5%)	20 (50.0%)	
Age			
Mean±SD	55.32±13.64	50.72±12.53	0.120
Range	33-77	26-73	
Marital status			
Married	30 (75.0%)	29 (72.5%)	0.799
Single	10 (25.0%)	11 (27.5%)	
Mean disease duration (month)	11.28±14.67		

Table 2. Comparison of DASS-21 scale scores in MF and control groups

Characteristics	Patient group		Control group		P
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
DASS-21-Depression	4.68±0.63	4.0 (0-18)	4.20±1.92	4.0 (0-8)	
DASS-21-Anxiety	4.28±0.56	3.5 (0-16)	4.15±2.04	4.0 (0-8)	p> 0.05
DASS-21-Stress	4.95±0.61	4.0 (0-18)	4.48±1.85	5.0 (0-8)	
DASS-21-Total	13.9±1.72	13.0 (0-52)	12.83 ± 0.76	14.0 (1-19)	

The mean total Skindex-29 questionnaire score for the MF patients was 23.62 ± 15.40 (median=20.68). The mean symptom subscale of Skindex-29 was 33.92 ± 17.04, while emotion subscale was 25.43 ± 18.99 and functioning subscale was 16.09 ± 15.37.

When the correlation between Skindex-29 subscales according to gender was examined, the symptom and emotion subscale scores were found to be statistically higher in female MF patients ($p \leq 0.05$). There were no significant differences between the stage of the disease and the Skindex-29 subscales ($p> 0.05$) (Table-3).

Table 3: Correlation of the Skindex-29 subscale scores between gender and stage of the disease

Skindex-29 domains	Sex		p	Stage			p
	Female	Male		1A	1B	2A	
Symptom	41.9 ± 4.1 42.8 (0-67)	26.7±2.7 32.1 (7.1-46.4)	**0.03**	31.3±2.9 32.1 (0-67.8)	44.2±6.3 39.2 (32.1-64.2)	41.0±11.1 41.0 (14.2-67.8)	> 0.05
Emotion	34.21 ± 5.29 32.5 (2.5-90.0)	17.50 ± 2.01 17.50 (0-32.5)	**0.006**	24.83±3.64 22.5 (0-90.0)	22.0±5.14 20.0 (10.0-40.0)	34.3±8.1 37.5 (12.5-50.0)	> 0.05
Functioning	20.50 ± 4.44 14.5 (0-66.6)	12.10 ± 1.91 8.33 (0-31.2)	0.27	14.9±2.8 12.5 (0.0-66.6)	18.3±4.85 16.6 (8.3-33.3)	22.3±7.6 21.8 (4.1-41.6)	> 0.05

**: Number are displayed as mean± standard deviation and median (range).*

Significant positive correlation was detected between age and symptoms and functioning subscale scores ($p \leq 0.05$). Additionally, DASS-21 total scores were positively correlated with all Skindex-29 subscale scores ($p \leq 0.05$) (Table-4).

Table 4. Correlation of Skindex-29 subscale scores between age, duration of disease and DASS-21 total scores in MF patients

Skindex-29 domains	Age	Duration of disease	DASS-21 score (total)
Symptoms	p=0.01*	p=0.227	p=0.000*
	r=0.404	r=0.160	r=0.546
Emotion	p=0.08	p=0.919	p=0.000*
	r=0.277	r=-0.017	r=0.658
Functioning	p=0.001*	p=0.360	p=0.000*
	r=0.486	r=0.149	r=0.558

**: Positive correlation between the variables.*

3. Discussion

MF is a chronic cutaneous T-cell lymphoma typically presents in its early stage. The disease can be difficult to diagnose in its earliest stages because it may mimic a number of benign skin disorders. Although MF is a disease with low risk of progression and a slowly progressing course, for which no effective cure is available. MF is a disease that is difficult to differentiate and negatively affects the quality of life of patients. Patients were almost always affected by a wide range of symptoms such as redness, scaling and pruritus due to the disease (5, 7).

Psychological morbidity is common in patients with hematologic malignancies and could negatively influence patients' life. Frequent hospital visits, diagnostic procedures, treatment-related side effects, and fear of death may cause psychiatric conditions such as depression and anxiety in MF patients (6, 7). In our study, we evaluated the DASS-21 scores of MF patients and compared it with a group of healthy controls. To the best of our knowledge, there is no study evaluated the depression, anxiety and stress status in MF patients using the DASS-21 scale. In our study, the mean depression, anxiety and stress subscales of DASS-21 were 4.28, 4.28 and 4.95, respectively. However, we found no significant difference in DASS-21 scores between MF patients and controls. Several studies on chronic inflammatory diseases such as acne and psoriasis have found higher DASS-21 scores than our study (13-15). This may be due to the fact that most of our MF patients were in the early stages which has a good response to skin-directed therapies. In addition, acne and psoriasis can affect visible areas such as

the face, which can cause further deterioration in the psychological status of patients.

In our study, health-related quality of life was evaluated using the Skindex-29 questionnaire in MF patients. In the literature, there are several studies measured the impact of skin disease on health-related quality of life using the Skindex-29 questionnaire (16-19), although it does not comprise cancer-spesific items. Sampogna et al. reported a study comparing the quality of life in patients with cutaneous lymphomas and other dermatological diseases. This study showed that patients with even more severe stages of cutaneous lymphoma reported a similar quality of life impairment to psoriasis patients. Additionally, they revealed that emotional functioning was similar to the patients with vitiligo. They concluded that this may be related to the visible aspect of the psoriasis and vitiligo diseases (16).

The median global Skindex-29 questionnaire score of our study population was 20.68. When the Skindex-29 subscale scores in our study were compared with the literature (20, 21), the symptom subscale scores were found to be similar, while the emotion and functioning subscale scores were found to be lower than these studies. Female MF patients had significantly worse symptom and emotion Skindex-29 subscale scores compared to male patients. Recently, a large cohort study also demonstrated that the greatest impact on symptoms and emotions subscales of the Skindex-29 in patients with cutaneous T cell lymphoma (22). Molloy et al. reported a study for identifying the factors associated with poorer health-related quality of life in a large study population of 236 newly diagnosed MF patients. Similarly, they found that as measured by Skindex-29, female patients with MF have a significantly worse symptom and emotion subscale scores compared to male patients (19). These gender differences regarding health-related quality of life in patients with cutaneous lymphoma have also been demonstrated (16, 18). Eder et al. evaluated the illness perception in primary cutaneous T-cell lymphomas and they showed that women perceive the disease as more chronic than men (18). Sampogna et al. showed that a worse quality of life was observed in female patients for all the subscales of Skindex-29 in patients with cutaneous lymphomas (16). It has been reported that quality of life has been more impaired in female patients with inflammatory skin diseases such as psoriasis, atopic dermatitis and vitiligo, as well as in non-Hodgkin lymphoma compared to male patients (23-26). This may be related to the women tend to be more emotionally affected by their disease than men.

It is expected that stage of MF negatively correlated the patients' quality of life. Previous studies showed that quality of life was more affected in patients with advanced-stage MF (16, 22, 27, 28). It is also reported that patients with advanced-stage disease have more impairment in general health status, emotional well-being, fatigue and insomnia (16). However, Holahan et al. used Skindex-16 for evaluating the health-related quality of life and did not find a direct relationship between stage and quality of life. They suggested that this may be due to the earlier stage of disease of their patients (29). Similarly, we did not find a positive correlation between stage of the disease and Skindex-29 subscale scores. This may be because of our study included only patients with early-stage disease, and 77.5% of them were in stage 1A, where there were a limited number of lesions.

In our study, we also revealed a positive correlation between age and symptoms and functioning subscale scores in early-stage MF patients. Several studies also showed that younger patients with non-Hodgkin lymphoma have higher quality of life (30-32). Although most of our patients were at stage IA, elderly patients may have a reduced ability to cope with chronic skin diseases or manage symptoms. We also found that DASS-21 total scores were positively correlated with all Skindex-29 subscale scores in our MF patients. This indicates that psychological conditions such as depression, anxiety and stress that develop due to even the early-stage MF may lead to the worsening of the symptoms, emotions or functioning.

The limitations of our study are its a single-center design and the small sample size of MF patients including only Turkish population. Studying the quality of life and psychological health throughout the country may provide different insights into evaluation of patients.

In conclusion, this study demonstrated that female MF patients had more symptoms and emotional impairment related to disease. Additionally, elderly MF patients had more cutaneous symptoms and functional deterioration. Even in the early stages of MF, health related quality of life was more affected in patients with increased levels of depression, anxiety and stress. By improving the psychological health of MF patients, their quality of life can be

better. We are of the opinion that further prospective studies are needed to elucidate our results.

REFERENCES

1. Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood. 2019:18;133:1703-14.
2. Larocca C, Kupper T. Mycosis Fungoides and Sézary Syndrome: An Update. Hematol Oncol Clin North Am. 2019;33:103-120.
3. Zinzani PL, Ferreri AJ, Cerroni L. Mycosis fungoides. Crit Rev Oncol Hematol. 2008;65:172-82.
4. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007;110:1713-22.
5. Hodak E, Lessin S, Friedland R, Freud T, David M, Pavlovsky L, et al. New insights into associated co-morbidities in patients with cutaneous T cell lymphoma (mycosis fungoides). Acta Derm Venereol. 2013;93:451-5.
6. Demierre MF, Kim YH, Zackheim HS. Prognosis, clinical outcomes and quality of life issues in cutaneous T-cell lymphoma. Hematol Oncol Clin North Am. 2003;17:1485-1507.
7. Ottevanger R, van Beugen S, Evers AWM, Willemze R, Vermeer MH, Quint KD. Quality of life in patients with Mycosis Fungoides and Sézary Syndrome: a systematic review of the literature. J Eur Acad Dermatol Venereol. 2021;35:2377-87.
8. Engin B, Kecici AS, Uzun AO, Yalcin M. Psychiatric comorbidity, depression, and anxiety levels and quality of life of the patients with mycosis fungoides. Dermatol Ther. 2020;33:e13922.
9. Lovibond PF, Lovibond SH. The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behav Res Ther. 1995;33:335-43.
10. Saricam H. The psychometric properties of Turkish version of Depression Anxiety Stress Scale-21 (DASS-21) in health control and clinical samples. JCBPR. 2018;7:19-30.
11. Chren MM, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. J Invest Dermatol. 1996;107:707-13.
12. Aksu AE, Urer MS, Sabuncu I, Saracoglu ZN, Chren MM. Turkish version of Skindex-29. Int J Dermatol. 2007;46(4):350-5.
13. Namli MN, Gokcay H, Tas B, Balcioglu YH, Sagaltici E, Belli H. Association of clinical features and systemic immune inflammation index with psychological distress in acne vulgaris. Dusunen Adam J Psychiatr Neurol Sci. 2022;35:174-180.
14. Chag J, Javadekar A, Mukherjee SS, Chaudhury S, Saldanha D. Psychiatric Co-Morbidy and Quality of Life in Patients with Psoriasis in a Tertiary Care Hospital. J Int Med Sci Acad. 2022;35:337-43.
15. Iocca F, Burlando M, Angelo NL, Ragucci F, Pugi D, Parodi A, et al. Sexual functioning in patients with psoriasis: the role of body dissatisfaction and cognitive biases toward sexuality. J Sex Marital Ther. 2024;50:439-55.
16. Sampogna F, Frontani M, Baliva G, Lombardo GA, Alvetreti G, Di Pietro C, et al. Quality of life and psychological distress in patients with cutaneous lymphoma. Br J Dermatol. 2009;160:815-22.
17. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National cutaneous lymphoma foundation survey. Cancer. 2006;107:2504-11.
18. Eder J, Kammerstätter M, Erhart F, Mairhofer-Muri D, Trautinger F. Illness Perception in Primary Cutaneous T-cell Lymphomas: What Patients Believe About Their Disease. Acta Derm Venereol. 2016;96:381-5.
19. Molloy K, Jonak C, Woei-A-Jin FJSH, Guenova E, Busschots AM, Bervoets A, et al. Characteristics associated with significantly worse quality of life in mycosis fungoides/Sézary syndrome from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study. Br J Dermatol. 2020;182:770-9.
20. Herbosa CM, Semenov YR, Rosenberg AR, Mehta-Shah N, Musiek AC. Clinical severity measures and quality-of-life burden in patients with mycosis fungoides and Sezary syndrome: comparison of generic and dermatology-specific instruments. J Eur Acad Dermatol Venereol. 2020;34: 995-1003.
21. Porkert S, Lehner-Baumgartner E, Valencak J, Knobler R, Riedl E, Jonak C. Patients' Illness Perception as a Tool to Improve Individual Disease Management in Primary Cutaneous Lymphomas. Acta Derm Venereol. 2018;98:240-5.
22. Ortiz Romero PL, Kim YH, Molloy K, Quaglino P, Scarisbrick J, Thornton S, et al. Health-related quality of life in cutaneous T-cell lymphoma: A post hoc analysis of a phase 3 trial in mycosis fungoides and Sézary syndrome. J Eur Acad Dermatol Venereol. 2024 Sep 24.
23. Obradors M, Blanch C, Comellas M, Figueras M, Lizan L. Health-related quality of life in patients with psoriasis: a systematic review of the European literature. Quality of Life Research. 2016;25(11):2739-54.
24. Holm JG, Agner T, Clausen ML, Thomsen SF. Quality of life and disease severity in patients with atopic

dermatitis. J Eur Acad Dermatol Venereol. 2016;30:1760-7.

25. Hedayat K, Karbakhsh M, Ghiasi M, Goodarzi A, Fakour Y, Akbari Z, et al. Quality of life in patients with vitiligo: a cross-sectional study based on Vitiligo Quality of Life index (VitiQoL). Health Qual Life Outcomes. 2016;14:86.
26. Sarker SJ, Smith SK, Chowdhury K, Ganz PA, Zimmerman S, Gribben J, et al. Comparison of the impact of cancer between British and US long-term non-Hodgkin lymphoma survivors. Support Care Cancer. 2017;25:739-48.
27. Ottevanger R, van Beugen S, Evers AWM, Willemze R, Vermeer MH, Quint KD. Itch in patients with cutaneous T-cell lymphoma as a quality of life indicator. JAAD Int. 2022;9:57-64.
28. Demierre MF, Ferzli P, Miller D. Measuring HRQOL in patients with cutaneous T-cell lymphoma undergoing therapy with oral bexarotene and extracorporeal photopheresis. Arch Dermatol. 2007;143(5):659-61.
29. Holahan HM, Farah RS, Fitz S, Mott SL, Ferguson NN, McKillip J, et al. Health-related quality of life in patients with cutaneous T-cell lymphoma? Int J Dermatol. 2018;57:1314-19.
30. Jensen RE, Arora NK, Bellizzi KM, Rowland JH, Hamilton AS, Aziz NM. Health-related quality of life among survivors of aggressive non-Hodgkin lymphoma. Cancer. 2013;119:672-680.
31. Kim SH, Kim IR, Kim SH, Lee S, Ok O, Kim WS. Health-related quality of life in Korean lymphoma survivors compared with the general population. Ann Hematol. 2014;93:1531-1540.
32. Smith SK, Mayer DK, Zimmerman S, Williams CS, Benecha H, Ganz PA, et al. Quality of life among long-term survivors of non-Hodgkin lymphoma: a follow-up study. J Clin Oncol. 2013;31:272-9.

Osmangazi Journal of Med, 2025;47(1):102- 109
DOI: 10.20515/otd.1596794

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Bebek/Çocuk Temalı Reklamların Kadınların Depresyon, Anksiyete, Stres Düzeylerine Etkisi

The Effects of Baby/Child Themed Adverisements On Women's Depression, Anxiety and Stress Levels

[1]Melike Tunca Bal, [2]Yeliz Kaya

[1]Afyonkarahisar Devlet Hastanesi, Anestezi ve Reanimasyon Yoğun Bakım-2 Ünitesi, Afyonkarahisar, Türkiye
[2]Eskişehir Osmangazi Üniversitesi Sağlık Bilimleri Fakültesi, Hemşirelik Bölümü, Eskişehir, Türkiye

ORCID ID of the authors
MTB. 0000-0002-1103-5722
YK. 0000-0003-4277-3960

Correspondence / Sorumlu yazar:
Melike TUNCA BAL

Afyonkarahisar Devlet Hastanesi, Anestezi ve Reanimasyon Yoğun Bakım-2 Ünitesi, Afyonkarahisar, Türkiye

e-mail: meliketunca45@gmail.com

Etik Kurul Onayı: Çalışma Afyonkarahisar Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından onaylanmıştır. Karar no: 2022/604 Tarih: 02.12.2022
Telif Hakkı Devir Formu: Tüm yazarlar tarafından Telif Hakkı Devir Formu imzalanmıştır.
Yazar Katkısı: Veri toplama: MTB,YK. Konsept: MTB,YK Tasarım: MTB,YK. Veri İşleme: MTB,YK Analiz veya Yorum: MTB,YK. Literatür Taraması: MTB,YK Yazma: MTB,YK
Çıkar Çatışması Beyanı: Yazarlar arasında herhangi bir çıkar çatışması bulunmamaktadır.
Destek ve Teşekkür Beyanı: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received : 06.12.2024
Accepted : 30.12.2024
Published :02.01.2025

Abstract: While studies examining the effects of advertisements on children are frequently encountered in the literature, no studies have been found examining the effects of baby/child-themed advertisements on the differences in stress, anxiety and depression levels in the lives of infertile women, who are considered a particularly sensitive group. Examining the psychological reactions of infertile women when they see baby and child-themed advertisements is important in terms of supporting their coping systems. The aim of this study was to investigate the effects of baby/child-themed advertisements on women's depression, anxiety and stress levels. In this descriptive and analytical study, women were divided into 3 groups according to their pregnancy status: spontaneously pregnant women, those who became pregnant with assisted reproductive techniques and those who tried assisted reproductive techniques but could not become pregnant, and each group consisted of 30 people. The data were collected with the "Socio-Demographic Characteristics Data Form" and the "Depression, Anxiety, Stress Scale (DASS-42)" and then analyzed. When the mean scores of the women on the depression, anxiety and stress scales were compared and examined according to the groups, it was determined that the difference between the groups was statistically significant ($p<0.05$). It was determined that baby-themed advertisements increased the mean scores of the depression, anxiety and stress scales of women who tried Assisted Reproductive Techniques and could not get pregnant. It is important that infertile women in the sensitive group are provided with counseling services by health professionals so that they can develop coping strategies to prevent them from being negatively affected by the advertisement groups they will frequently encounter in daily life.
Keywords: Infertility, depression, anxiety, stress, advertising

Özet: Reklamların çocuklar üzerindeki etkilerinin incelendiği çalışmalar literatürde sıklıkla karşımıza çıkarken; özellikle hassas bir grupta değerlendirilen infertil kadınların yaşamlarındaki stres, anksiyete ve depresyon düzeylerindeki farklılıklara ilişkin bebek/çocuk temalı reklamların etkisinin incelendiği çalışmalara rastlanılmamıştır. İnfertil kadınların, bebek ve çocuk temalı reklamları gördüğünde vermiş oldukları ruhsal tepkilerin incelenmesi, baş edebilme sistemlerine destek olma açısından önem arz etmektedir. Bu çalışmada, Bebek/Çocuk temalı reklamların kadınların depresyon, anksiyete, stres düzeylerine etkisini araştırmak amaçlanmıştır. Tanımlayıcı ve analitik tipte yapılan bu çalışmada kadınlar, gebe kalma durumlarına göre; spontan gebe kalan kadınlar, yardımcı üreme tekniği ile gebe kalanlar ve yardımcı üreme tekniği deneyip gebe kalamayanlar şeklinde 3 gruba ayrılarak her bir grup 30 kişiden oluştu. Veriler "Sosyo-Demografik Özellikler Veri Formu" ve "Depresyon, Anksiyete, Stres Ölçeği (DASS-42)" ile toplandıktan sonra analiz edildi. Kadınların, depresyon, anksiyete, stres ölçeği puan ortalamaları gruplara göre kıyaslanarak incelendiğinde, gruplar arasındaki farklılığın istatistiksel açıdan anlamlı olduğu tespit edildi ($p<0,05$). Bebek çocuk temalı reklamların, Yardımcı Üreme Tekniklerini deneyip gebe kalamayan kadınların, depresyon, anksiyete ve stres ölçeği puan ortalamalarını artırdığı belirlendi. Hassas grupta yer alan infertil kadınlara, günlük yaşamda sıklıkla karşılaşacakları reklam gruplarından olumsuz etkilenmelerini önlemek için baş etme stratejileri geliştirebilmeleri adına sağlık profesyonelleri tarafından danışmanlık hizmeti verilmesi önem arz etmektedir.
Anahtar Kelimeler: İnfertilite, depresyon, anksiyete, stres, reklam

How to cite/ Atıf için: Bal Tunca M, Kaya Y. Bebek/Çocuk Temalı Reklamların Kadınların Depresyon, Anksiyete, Stres Düzeylerine Etkisi, Osmangazi Journal of Medicine, 2025;47(1):102-109

1. Giriş

İnfertilite; bebeğin doğmasıyla, aile soyunun devam ettiği düşüncesinin hâkim sürdüğü topluluklarda utanma, yetersizlik hissi, dışlanma, damgalanma, depresyon, kaygı yaşayan bireyleri; ailesel, psikolojik, ekonomik ve kültürel boyutta etkisi altına alan, strese neden olan yaşam krizi ve beklenilmeyen durum olarak adlandırılmaktadır (Wang vd., 2022; Fata & Tokat, 2017; Uğur, 2014). Kriz olarak adlandırılan bu durumun içerisinde kadınlara en fazla yük getiren ve onlar üzerinde etki oluşturan kısmı, bu sürecin yardımcı üreme tekniklerine ait olan kısmıdır (Yılmaz & Yeşiltepe Oskay, 2016).

Medya, kadınların yaşamında çevresindeki insanlarla olan ilişkilerine, aile ortamındaki eylem ve birlikteliklerine kadar bütün yaşamını etkileyebilme gücüne sahip olmaktadır. Eğitim düzeyinin, ekonomik gelir düzeyinin az olması bu etkilenmeyi fazlaca arttıran unsurlardır. Lakin bu etkilenme her zaman pozitif yönde olmamaktadır (Koparan, 2007). İnfertilite ve tedavi süreci başlı başına kriz etkisi oluşturan bir durum olarak görülürken, güncel pratikte bu krizin etkilerini artırdığı düşünülen çevresel faktörlerin arasında bulunan televizyon veya internettin de dahil olduğu sosyal medyanın herhangi bir alanında gördüğü; bebekler/çocuklar, bebek/çocuk fotoğrafları, videoları, oyuncak bebekler ve reklamlar, infertil kadınlarda depresyon, anksiyete ve stres düzeylerinin artmasını tetikleyebileceği düşünülmektedir.

İnfertilitenin bireylerde depresyon, anksiyete, stres düzeylerinin incelendiği çalışmalara literatürde rastlanmaktadır, ancak sosyal medyanın, reklamların, özellik arz eden infertil grubun üzerine etkilerini inceleyen bir çalışmaya literatürde rastlanmamıştır. Buradan yola çıkılarak çalışmamız planlanmıştır. Bu araştırmada da bebek/çocuk temalı reklamların kadınların depresyon, anksiyete, stres düzeylerine etkisini incelemek amaçlanmıştır. Çalışmanın araştırma soruları;

-Bebek/çocuk temalı reklam izleme durumlarına göre, spontan gebe kalan, YÜT ile gebe kalan ve YÜT ile gebe kalamayan kadınların Depresyon puan ortalamaları arasında istatistiksel açıdan anlamlı bir farklılık vardır / yoktur.

-Bebek/çocuk temalı reklam izleme durumlarına göre, spontan gebe kalan, YÜT ile gebe kalan ve YÜT ile gebe kalamayan kadınların Anksiyete puan ortalamaları arasında istatistiksel açıdan anlamlı bir farklılık vardır / yoktur.

- Bebek/çocuk temalı reklam izleme durumlarına göre, spontan gebe kalan, YÜT ile gebe kalan ve YÜT ile gebe kalamayan kadınların Stres puan ortalamaları arasında istatistiksel açıdan anlamlı bir farklılık vardır / yoktur.

Bu çalışma, Eskişehir Osmangazi Üniversitesi Sağlık Bilimleri Enstitüsü Hemşirelik Anabilim Dalı Yüksek Lisans Programı kapsamında 2024 yılında başarı ile tamamlanan yüksek lisans tez çalışmasına ait sonuçları içermektedir.

2. Gereç ve Yöntem

Araştırmanın Tipi: Tanımlayıcı tip.

Araştırmanın Evreni ve Örneklemi

Kurum izinleri alındıktan sonra bu çalışma, 12.12.2022 ile 05.06.2023 tarihleri arasında Kadın Hastalıkları ve Doğum Polikliniği ve Tüp Bebek Merkezine başvuru yapan, araştırmaya dahil edilme kriterlerine uyan (18-49 yaş aralığında, okur-yazar olma ve herhangi bir iletişim problemi olmayan, spontan gebe kalan kadınlar için gebeliğin 2.trimesterında olma, hekim tarafından tanı almış ruhsal ve sistemik bir rahatsızlığı olmama) ve çalışmaya gönüllü katılmayı kabul eden kadınlar ile bilgilendirilmiş gönüllü olur formu doldurularak yapıldı. Kadınlar gebe kalma durumlarına göre; spontan gebe kalan kadınlar, yardımcı üreme tekniği ile gebe kalanlar ve yardımcı üreme tekniği deneyip gebe kalamayanlar şeklinde 3 gruba ayrıldı. Literatürdeki benzer çalışmalar gözden geçirildikten sonra üç gruba ayrılacak katılımcı sayısı için Power analizi yapıldı. Bu analiz çalışması yapılırken Oğuz ve diğerleri (2019) tarafından yapılan çalışmadaki "DASS değerleri" baz alındı. DASS değerleri dikkate alındığında; %95 güven (1-α), %95 test gücü (1-β), f=0,335 etki büyüklüğü ve testin gücü minimum %80 alındığında her bir grupta 30 olmak üzere toplamda 90 katılımcının çalışmaya dahil edilmesi gerektiği saptandı. G*Power V. 3.1.9.6 programı kullanılarak örnek genişliği hesaplandı (Oğuz vd., 2019).

Veriler "Sosyo-Demografik Özellikler Veri Formu" ve "Depresyon, Anksiyete, Stres Ölçeği (DASS-42)" ile toplandı.

Yapılan çalışmada, araştırma ve yayın etiğine uyulmuştur.

Sosyo-demografik Özellikler Veri Formu

Araştırmacı tarafından oluşturulan bu formda katılımcıların yaşı, eşlerinin yaşı, eğitim durumları, eşlerinin eğitim durumları, meslekleri ve eşlerinin mesleği, evlilik süresi, aile tipi, yaşadıkları yer gibi sosyodemografik bilgiler için 15 soru, obstetrik öykü, infertilite öyküsü olanlar için 5 soru (Kaya vd., 2016) ve televizyon/medya reklamları için son bir haftadaki duygu ve düşüncelerini ölçmeye yönelik, RTÜK'ün televizyon ve reklamlar ile ilgili kaynak soruları baz alınarak taranan literatür doğrultusunda hazırlanan 10 soru bulunmaktadır (RTÜK, 2018).

Depresyon, Anksiyete, Stres Ölçeği (DASS-42)

Lovibond ve Lovibond (1995) tarafından geliştirilen, Bilgel ve Bayram (2010) tarafından Türkçe'ye uyarlanarak güvenirliği saptanan Depresyon, Anksiyete, Stres Ölçeği ilk 14 maddesi depresyon, sonraki 14 maddesi anksiyete ve son 14 maddesi stres kategorilerine ait olmak üzere toplam 42 maddeden oluşmaktadır. Ölçek 0 hiçbir zaman, 1 bazen ve ara sıra, 2 oldukça sık ve 3 her zaman şeklinde 4'lü likert tipi derecelendirmeden oluşmaktadır. DASS-42'nin yönergesinde, bireyden her bir maddeyi son 7 gün içinde kendisi için ne kadar uygun olduğuna göre cevaplaması istenmektedir. Depresyon, anksiyete ve stres boyutlarının her birinden alınan puanların yüksek olması, bireyin ilgili probleme sahip olduğunu ortaya koymaktadır. Ters madde bulunmayan ölçeğin toplam puanları her bir alt boyut için 0 ile 42 arasında değişmektedir. Depresyon için 0-9 puan arası normal, 10-13 puan arası hafif, 14-20 puan arası orta, 21-27 puan arası ileri, 28 puan ve üzeri ise çok ileri düzeyde depresyon olarak kabul edilmektedir. Anksiyete için 0-7 puan arası normal, 8-9 puan arası hafif, 10-14 puan arası orta, 15-19 puan arası ileri, 20 puan ve üzeri ise çok ileri düzeyde anksiyete olarak kabul edilmektedir. Stres için ise 0-14 puan arası normal, 15-18 puan arası hafif, 19-25 puan arası orta, 26-33 puan arası ileri, 34 puan ve üzeri ise çok ileri düzeyde stres olarak kabul edilmektedir (Bilgel & Bayram, 2010).

İstatistiksel Analiz

Analizlere başlamadan önce sayısal verilerin normal dağılıma uygunluğu Skewness (çarpıklık) ve Kurtosis (basıklık) testleri, Histogram ve Q-Q Plot grafikleri ile incelendi. Yapılan analizler neticesinde verilerin normal dağılımdan geldiği görüldü. Kategorik veriler frekans ve yüzde değerleri ile gösterilirken sayısal veriler normallik varsayımını sağlaması sebebiyle ortalama ve standart sapma değerleriyle gösterildi. Veri analizi yapılırken, iki bağımsız grup karşılaştırması için "Independent Sample T Testi", ikiden fazla bağımsız grup olması durumunda "ANOVA" Testi kullanıldı. ANOVA testi sonucunda anlamlı farklılık bulunan sonuçlarda farklılığın kaynağını tespit etmek amacıyla varyanslar homojen ise Tukey, varyanslar homojen değil ise Tamhane Testi kullanıldı. Kategorik veriler arasındaki ilişkiye bakabilmek için Ki-Kare test istatistiğinden yararlanıldı. Anlamlı farklılık bulunan gruplar için Bonferroni düzeltmesi yapılarak hangi kategoriler arasında farklılık olduğu saptandı ve tüm analizlerde farklılıklar "a,b,c" harfleri ile gösterildi. Gruplara ait gözlem değerlerinin 30'un altında olduğu durumlarda iki bağımsız grup karşılaştırılması için Mann-Whitney U Testi, ikiden fazla bağımsız grup olması durumunda Kruskal-Wallis Testi kullanıldı. İk, kategorik değişken arasındaki ilişki Ki-Kare Testi ile analiz edildi, gözlem değeri 5'in altında olduğu durumlarda Fisher Exact anlamlılık değeri kullanıldı. Tüm testler için istatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edildi.

3. Bulgular

Araştırmaya dahil edilen kadınlardan, Spontan gebelik yaşayan kadınların yaş ortalaması 26,37±4,27, YÜT ile gebe kalanların 33,00±4,35 ve YÜT ile gebe kalamayan kadınların ise 33,60±5,05 olarak bulundu. Kadınların eğitim durumları, çalışma durumları, eşlerin eğitim durumu, eşlerin çalışma durumu, gelir durumu, yaşanılan yer, aile tipi, sigara ve alkol kullanım durumlarına ait dağılımlar gruplar arasında istatistiksel açıdan anlamlı farklılık göstermemektedir ($p>0,05$). YÜT ile gebe kalan kadınların ortalama infertilite süresi 4,27±2,70, YÜT deneyen ancak gebe kalamayan kadınların ortalama infertilite süresi ise 5,73±3,53 olarak elde edildi ($p>0,05$).

Tablo-1. Bebek-Çocuk Temalı Reklamlara İlişkin Bulguların Gruplara Göre Dağılımları

		Grup							
		Spontan Gebelik		YÜT ile Gebelik		YÜT Deneyen Ancak Gebelik Olmayan			
		N	%	N	%	N	%	χ^2	p
Bebek/çocuk temalı reklamlarda verilen ilk tepki	Reklam atlamak/ kanalı değiştirmek	3[a]	10,0%	9[b]	30,0%	14[c]	46,7%	20,68	**<0,001**
	Biraz izleyip bırakmak	14[a]	46,7%	19[b]	63,3%	13[a]	43,3%		
	Reklam bitene kadar izlemek	13[a]	43,3%	2[b]	6,7%	3[b]	10,0%		
Bebek/çocuk temalı reklam izleme süresi (günlük/dakika)	1-5 dk	17[a]	56,7%	29[b]	96,7%	24[ab]	80,0%	14,01	**<0,001**
	6-10 dk	10[a]	33,3%	1[b]	3,3%[b]	6[ab]	20,0%[c]		
	10 dk üzeri	3[a]	10%	0[a]	0,0%	0[a]	0,0%		

*χ^2 = Ki-Kare Testi; p<0,05

*a,b,c harfleri Posthoc analizi sonucunu temsil etmektedir. Farklı harfler arasında istatistiksel olarak anlamlı farklılık görülmektedir. Aynı harfler arasında farklılık bulunmamaktadır.

Bebek-çocuk temalı reklamlara verilen ilk tepkiler gruplar arasında istatistiksel açıdan anlamlı farklılığa sahiptir (p<0,05). Spontan gebe kalan kadınların %10,0'ı reklam atlamak/kanalı değiştirmek cevabını verirken bu oran YÜT ile gebe kalanlarda %30,0, YÜT deneyip gebe kalamayan kadınlarda ise %46,7 olarak elde edildi. YÜT deneyip gebe kalamayan kadınlarda reklamı atlama kanalı değiştirme oranı en yüksektir. Bebek-çocuk temalı reklam izleme süreleri ile gruplar arasında istatistiksel açıdan anlamlı farklılığa sahiptir (p<0,05). Spontan gebe kalan kadınların %10,0'ı 10 dk ve üzeri izleyebiliyorken bu oran YÜT ile gebe kalabilen ve kalamayan kadınlarda %0,0'dır (Tablo-1).

Tablo-2. Depresyon-anksiyete-stres ölçeği alt kategori puan ortalamalarına ilişkin verilerin gruplar arasında karşılaştırılması

	Grup							
	Spontan Gebelik		YÜT ile Gebelik		YÜT Deneyen Ancak Gebelik Olmayan			
	n	%	n	%	n	%	χ^2	p
Depresyon								
Normal (0-9)	29[a]	96,7%	9[b]	30,0%	1[c]	3,3%	74,559	**<0,001**
Hafif (10-13)	0[a]	0,0%	6[b]	20,0%	1[a,b]	3,3%		
Orta (14-20)	1[a]	3,3%	9[b]	30,0%	8[b]	26,7%		
İleri (21-27)	0[a]	0,0%	6[b]	20,0%	13[b]	43,3%		
Çok ileri (28+)	0[a]	0,0%	0[a]	0,0%	7[b]	23,3%		
Anksiyete								
Normal (0-7)	23[a]	76,7%	13[b]	43,3%	1[c]	3,3%	47,964	**<0,001**
Hafif (8-9)	4[a]	13,3%	2[a]	6,7%	1[a]	3,3%		
Orta (10-14)	3[a]	10,0%	0[a]	0,0%	5[a]	16,7%		
İleri (15-19)	0[a]	0,0%	5[a,b]	16,7%	8[b]	26,7%		
Çok ileri (20+)	0[a]	0,0%	10[b]	33,3%	15[b]	50,0%		
Stres								
Normal (0-14)	22[a]	73,3%	8[b]	26,7%	1[c]	3,3%	54,105	**<0,001**
Hafif (15-18)	7[a]	23,3%	8[a]	26,7%	2[a]	6,7%		
Orta (19-25)	1[a]	3,3%	12[b]	40,0%	16[b]	53,3%		
İleri (26-33)	0[a]	0,0%	2[a]	6,7%	11[b]	36,7%		
Çok ileri (34+)	0	0,0%	0	0,0%	0	0,0%		

Ki-Kare Testi; Fisher Exact Testi; p<0,05

*a,b,c harfleri Posthoc analizi sonucunu temsil etmektedir. Farklı harfler arasında istatistiksel olarak anlamlı farklılık görülmektedir. Aynı harfler arasında farklılık bulunmamaktadır.

Spontan gebe kalan kadınlar, YÜT ile gebe kalan kadınlar ve YÜT ile gebe kalamayan kadınların depresyon, anksiyete, stres ölçeği alt kategori puan ortalamaları arasındaki farklılık anlamlı bulunmuştur (p<0,05) (Tablo-2).

Bebek çocuk temalı reklamlara verilen tepkilere ilişkin kadınların depresyon, anksiyete, stres puan ortalamaları arasındaki farklılığın gruplar arası incelenmesi tek tek yapıldığında;

Bebek/Çocuk temalı reklamları izleyince üzülüyorum, Bebek/Çocuk temalı reklamları izleyince kanalı değiştiriyorum, Bebek/Çocuk temalı reklamları izleyince umutsuzluğa kapılıyorum, Bebek/Çocuk temalı reklamları izleyince kendimi suçlu/yetersiz hissediyorum, Bebek/Çocuk temalı reklamları izleyince kendimden utanıyorum, Bebek/Çocuk temalı reklamları izleyince terliyorum, kalp atışım hızlanıyor, bayılacak gibi oluyorum, Bebek/Çocuk temalı reklamları izleyince bebeğimin olması için dua ediyorum ve Bebek/Çocuk temalı reklamları izleyince acı ya da kayıp duygusu hissediyorum ifadelerine evet diyenlerin depresyon düzeyleri gruplara göre istatistiksel açıdan anlamlı farklılık göstermektedir ($p<0,05$). Tüm bu ifadelere evet diyenlerin depresyon ortalamaları incelendiğinde en düşük ortalamanın Spontan gebelik yaşayan kadınların grubunda, en yüksek ortalamanın ise YÜT deneyen ancak gebelik yaşayamayan kadınların grubunda olduğu saptandı.

Bebek/Çocuk temalı reklamları izleyince üzülüyorum, Bebek/Çocuk temalı reklamları izleyince kanalı değiştiriyorum, Bebek/Çocuk temalı reklamları izleyince kendimden utanıyorum, Bebek/Çocuk temalı reklamları izleyince bebeğimin olması için dua ediyorum ve Bebek/Çocuk temalı reklamları izleyince acı ya da kayıp duygusu hissediyorum ifadelerine evet diyenlerin anksiyete düzeyleri gruplara göre istatistiksel açıdan anlamlı farklılık göstermektedir ($p<0,05$). Tüm bu ifadelere evet diyenlerin anksiyete ortalamaları incelendiğinde, en düşük ortalamanın Spontan gebelik yaşayan kadınların grubunda, en yüksek ortalamanın ise YÜT deneyen ancak gebelik yaşayamayan kadınların grubunda olduğu saptandı.

Bebek/Çocuk temalı reklamları izleyince üzülüyorum, Bebek/Çocuk temalı reklamları izleyince ağlamaya başlıyorum, Bebek/Çocuk temalı reklamları izleyince kanalı değiştiriyorum, Bebek/Çocuk temalı reklamları izleyince umutsuzluğa kapılıyorum, Bebek/Çocuk temalı reklamları izleyince kendimi suçlu/yetersiz hissediyorum, Bebek/Çocuk temalı reklamları izleyince kendimden utanıyorum, Bebek/Çocuk temalı reklamları izleyince terliyorum, kalp atışım hızlanıyor, bayılacak gibi oluyorum, Bebek/Çocuk temalı reklamları izleyince bebeğimin olması için dua ediyorum ve Bebek/Çocuk temalı reklamları izleyince acı ya da kayıp duygusu hissediyorum ifadelerine evet diyenlerin stres düzeyleri gruplara göre istatistiksel açıdan anlamlı farklılık göstermektedir ($p<0,05$). Tüm bu ifadelere evet diyenlerin depresyon ortalamaları incelendiğinde en düşük ortalamanın Spontan gebelik yaşayan kadınların grubunda, en yüksek ortalamanın ise YÜT deneyen ancak gebelik yaşayamayan kadınların grubunda olduğu saptandı.

4. Tartışma

Literatür incelendiğinde genel reklamların kadınlar üzerindeki etkilerini ortaya koyan çalışma ya da raporlara rastlanmışken; özellikle hassas bir grup olan infertil kadınlarda bu hassasiyet üzerinden doğrudan ya da dolaylı etki gösterebilecek bebek ve çocuk temalı reklamların etkisi spesifik bir biçimde ölçülmemiştir (Koparan, 2007). Yapılan araştırma bu bakımdan bir ilk olması yönünde özellik gösterirken, yaşamın içinde sıklıkla karşımıza çıkan özellikli reklamların infertilite problemi yaşayan kadınlara soru olarak yöneltilmesi neticesinde kendilerindeki yansımalarını ifade etmekte ve bunun farkına varmakta zorlandıkları gözlenmiş, sonuçlar da bu doğrultuda sınırlı kalmıştır. Dolayısıyla bu bölüm bebek ve çocuk temalı reklamların genel etkilerini inceleyen bulgularla tartışılmaktadır.

Şener Aslan'ın (2022), annelerin bebeklerini emzirme veya anne sütüyle beslemeye yönelik karar vermesinde medya ve reklamların etkisinin nasıl olabileceği konusunda yaptığı çalışma bulgusuna göre, sosyal medyada ve televizyon reklamlarında anne sütünü tavsiye eden gönderilerin, annelerin bebeklerini emzirmeye ve anne sütü vermeye yönelttiğini ve bu isteği artırdığı sonucunu paylaşmaktadır. Çalışmanın farklı bir sonucunda da formül mama reklamlarının emzirme üzerinde etki etmediğini ancak emzirmede sorun yaşayan anneler için farklı bir seçenek olarak görülebileceği sonucunu iletmektedir (Şener Aslan, 2022). Amerika'da yapılan bir çalışmada, formül mama ve formül sütün pazarlanması konusunda araştırma yapılmış ve sonucunda, formül mamaların tanıtılmasında çeşitli etkileyici reklamların ve farklı yolların kullanarak emzirme oranlarında ciddi şekilde negatif etki oluşturduğunu, hedef kitle olarak kadınları odağına alarak, devam sütlerinin yüksek oranda pazarlanmasının arttığını bildirmektedirler (Harris & Pomeranz, 2020).

Literatüre bakıldığında, bebek/çocuk temalı reklamların günlük/dakika bazında izlenme sürelerinin incelendiği çalışmalara

rastlanılmamaktadır. Yapılan bu araştırma sonucunda, bebek/çocuk temalı reklamları günlük/dakika bazında izleme sürelerine bakıldığında, her üç grupta da çoğunluğunun 1-5 dakika arasında olduğu ve oranlarının sırasıyla, spontan gebe kalan kadınlarda %56,7, YÜT ile gebe kalan kadınlarda %96,7, YÜT deneyen ancak gebe kalamayan kadınlarda %80,0 tespit edildi. Bebek-çocuk temalı reklam izleme süreleri ile gruplar arasında istatistiksel açıdan anlamlı farklılığa sahiptir. Spontan gebe kalan kadınların %10'u 10 dk ve üzeri reklamları izleyebiliyorken bu oran YÜT ile gebe kalabilen ve kalamayan kadınlarda %0'dır. Farklılık spontan gebe kalan kadınların grubundan kaynaklanmaktadır. Bu farklılık bizlere, YÜT deneyip gebe kalamayan kadınların bebek ve çocuk temalı reklamları fark ettikleri anda kanal değiştirdiklerini ancak bu reklamları fark etme sürelerinin baş etme mekanizmalarının devreye girmesinden kaynaklı biraz uzun sürebildiğini göstermektedir.

İnfertilitenin sebep olduğu ruhsal rahatsızlıklardan biri de depresyondur. Amerika'da infertil ve sağlıklı kadınlar üzerinde yapılan bir incelemede, incelemeye katılan 19 infertil kadının 12'sinde, 20 sağlıklı kadının 4'ünde depresyon bulgularının tespit edildiği iletilmektedir. Araştırmanın devamında infertilite kaynağı belli olmayan kadınlarda depresyon bulgusunun daha fazla olduğu sonucu iletilmektedir (Meller vd., 2002). Benzer bir şekilde Afrika'da yapılan bir çalışmada, infertilite biriminde takip edilen 199 kadın ile gebe takip biriminde takip edilen 200 gebe kadının duygusal stres düzeyleri karşılaştırılıp sonucunda, infertil kadınlarda depresyon görülme yaygınlığının %52 olduğu, gebe kadınlarda da %9,5 olduğu bildirilmektedir (Sulyman & Kuranga, 2022). Ülkemizde yapılan çalışmalarda da benzer şekilde sonuçlar bildirilmektedir (Yangın vd., 2016; Göker vd., 2018; Erdemoğlu & Aksoy Derya, 2022; Fata & Tokat, 2021). Çalışmamızda YÜT ile gebe kalamayan kadınların depresyon düzeyleri, spontan gebe kalan kadınlar ve YÜT ile gebe kalan kadınlardan daha yüksek bulundu. Çalışmamızın sonuçları ile literatürdeki çalışmaların sonucu benzerlik göstermektedir. İnfertil kadınlarda, annelik duygusunu yaşayamamaları, yapılan tedavilerin olumsuz sonuçlanması, infertilite süresinin uzun olması gibi çeşitli nedenlerin bu sonuçları ortaya çıkardığı ve psikolojik tepkilerden birisi olan depresyon belirtilerinin görülme olasılığını artırdığı düşünülmektedir.

İnfertil kadınlarda depresyon ve anksiyete düzeyini belirlemek amacıyla yapılan farklı bir çalışmada, depresyon görülen kadınların oranının %58, anksiyete görülen kadınların oranının %24, hem depresyon hem anksiyete görülen kadın oranının ise %24 olduğu belirtilmektedir. Depresyon ve anksiyete yaşayan kadınların, toplum tarafından kendilerinin dışlanmış hissettikleri belirtilmektedir. Bu olumsuz durum sosyokültürel yaşamlarında sıkıntılara, ekonomik zorluklara ve yaşam standartlarının azalmasına neden olabilmektedir (Dadhwal vd., 2022). Çin'de 842 infertil kadınla yapılan bir çalışmada, IVF tedavisi alan bireylerin %39,4'ünün anksiyete, %28,5'inin depresyon belirtilerini gösterdikleri bildirilmektedir (Xu vd., 2017). Bizim çalışmamızda ise YÜT ile gebe kalamayan kadınların anksiyete ortalaması, YÜT ile gebe kalan kadınların ve spontan gebe kalan kadınların anksiyete ortalamasından daha yüksek olduğu ve anksiyete düzeyleri arasında anlamlı farklılık olduğu tespit edildi.

Tedavilerin başarısızlıkla sonuçlanması, tekrarlayan işlemlerin ve tedavilerin olması, toplum tarafından hissedilen psikolojik baskı, işlem maliyetinin ekonomik yükünün fazla olması, sonuçlanamayan hayaller infertil kadınlarda anksiyete seviyesinin yükselmesine neden olabilmektedir (Fassino vd., 2002). Literatürde yer alan çalışmalar gözden geçirildiğinde, yaptığımız çalışmanın bu sonucu literatür ile uyumludur.

Türkiye'de 577 primer infertil kadınla yapılan bir çalışmada, kendinden kaynaklı infertilite durumunu yaşayan kadınların, oldukça fazla düzeyde stres yaşadıkları belirtilmektedir. Kadın kaynaklı infertilitesi olan kadınlar kendilerini yetersiz, kusurlu ve eksik görüp, etraflarından baskı hissetmekte, ekonomik anlamda çevresinden destek görememekte, tedavinin olumsuz sonuçlanmasıyla da ümitsizliğe sürüklenmekte ve bu durumda stres düzeylerinde oldukça artış görülmektedir (Sis Çelik & Kırca, 2018). Literatürde benzer nitelikteki çalışmalarda, infertil kadınlarda stres düzeylerinin yüksek oranda görüldüğü bildirilmektedir (Kutlu & Varışoğlu, 2021; Taşkın vd., 2016; Kamışlı vd., 2021; Shahraki vd., 2019). Çalışmamızda YÜT ile gebe kalamayan kadınların stres düzeyleri, spontan gebe kalan kadınlar ve YÜT ile gebe kalan kadınlardan daha yüksek bulundu. Üç gruptaki kadınların stres düzeyleri arasında farklılık bulunmaktadır. Çalışma bulgularımız, literatürde yer alan çalışma sonuçları ile benzerlik göstermektedir. Çalışmamızda YÜT deneyen ancak gebe kalamayan kadınların ortalama depresyon, anksiyete, stres

düzeyleri karşılaştırıldığında, sırasıyla en fazla oranda stresin görüldüğü, sonrasında depresyon ve anksiyete görüldüğü tespit edildi.

5. Sonuç

Çalışma sonucunda her üç gruptaki kadınların bebek çocuk temalı reklamlara verdikleri ilk tepkileri ve bebek-çocuk temalı reklam izleme sürelerinin gruplar arasında istatistiksel açıdan anlamlı farklılığa sahip olduğu tespit edildi.

Spontan gebe kalan kadınlar, YÜT ile gebe kalan kadınlar ve YÜT ile gebe kalamayan kadınların depresyon, anksiyete, stres ölçeği alt kategori puan ortalamaları arasında istatistiksel açıdan anlamlı farklılığa sahip olduğu tespit edildi.

İnfertilite tanısı alan kadınlar ile infertilite tanısı almış YÜT uygulanmış başarısız sonuçlanmış olan kadınların; günlük yaşamda sıklıkla karşılaşacakları reklam gruplarından olumsuz etkilenmelerini önlemek adına çözüm önerileri sunulmalı ve baş etme stratejileri geliştirmeleri sağlanmalıdır. Bu alanda daha geniş çaplı araştırmaların yapılması önerilmektedir. Sosyal medyada yer alan özellikli reklamların kadın üzerindeki olumsuz etkilerini en aza indirmek adına; sosyal medya maruziyetinin azaltılması, ekran sürelerinin kısaltılması gibi önerilerin temelde yer aldığı, desteğe ihtiyaç duyan kadınların tespiti ve ilgili alanlara psikososyal destek için yönlendirilmesi, psikososyal destek sistemlerinin aile, çevre, sağlık profesyonelleri tarafından farkındalığının oluşması ve oluşturulması önem arz ettiğinden sosyal duyarlılığın geliştirilmesi önerilmektedir.

KAYNAKLAR

1. Wang, Y., Fu, Y., Ghazi, P., Gao, Q., Tian, T., Kong, F., Zhan, S., Liu, C., Bloom, D. E., & Qiao, J. Prevalence of intimate partner violence against infertile women in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Global Health, 2022:10(6), e820-e830.
2. Fata, S., & Tokat, M. A. Fertilite desteği alan kadınların stresini azaltmada hipnofertilite'nin kullanımı. Dokuz Eylül Üniversitesi Hemşirelik Fakültesi Elektronik Dergisi, 2017:10(1), 60-66.
3. Uğur, A. S. İnfertilite tedavisi alan kadınlarda üreme problemlerinin fiziksel, duygusal, sosyal ve ilişkisel yaşam alanlarına etkisi [Yüksek Lisans Tezi, İstanbul Bilim Üniversitesi Sağlık Bilimleri Enstitüsü]. YÖK Ulusal Tez Merkezi, 2014.
4. Yilmaz, T., & Yeşiltepe Oskay, U. The Copenhagen Multi-centre Psychosocial Infertility (COMPI) fertility problem stress and coping strategy scales: A psychometric validation study in Turkish infertile couples. International Journal of Caring Sciences, 2016:9(2), 452-562.
5. Koparan, N. Medyanın kadınlar üzerindeki etkisi [Yüksek Lisans Tezi, Gazi Üniversitesi Eğitim Bilimleri Enstitüsü]. YÖK Ulusal Tez Merkezi, 2007.
6. Oğuz, S., Keskin Dilbay, N., Çeliktaş, E., Balcılar, R., & Polat, M. G. Effects of progressive muscle relaxation exercises on stress, sleep quality and exercises capacity in young adults. Journal of Health Science and Profession, 2019:6(3), 534-544.
7. Kaya, Y., Kizilkaya Beji, N., Aydin, Y., & Hassa, H. The effect of healthpromoting lifestyle education on the treatment of unexplained female infertility. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2016:207, 109–114.
8. Radyo Televizyon Üst Kurulu (RTÜK). (2018). Televizyon İzleme Eğilimleri Araştırması-2018. Kamuoyu, Yayın Araştırmaları ve Ölçme Dairesi Başkanlığı, Ankara. Erişim Tarihi:11.11.2023.
9. Lovibond, P. F., & Lovibond, S. H. The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the beck depression and anxiety inventories. Behavioral Research and Therapy, 1995:33, 335-343.
10. Bilgel, N., & Bayram, N. Depresyon Anksiyete Stres Ölçeğinin (DASS-42) Türkçeye uyarlanmış şeklinin psikometrik özellikleri. Archives of Neuropsychiatry, 2010:47, 118-126.
11. Şener Aslan, A. G. Annelerin bebeklerini emzirme ve anne sütüyle besleme kararları üzerinde medya ve reklamların rolü; niteliksel çalışma [Yüksek Lisans Tezi, Ege Üniversitesi Sağlık Bilimleri Enstitüsü]. YÖK Ulusal Tez Merkezi, 2022.
12. Harris, J. L., & Pomeranz, J. L. . Infant formula and toddler milk marketing: opportunities to address harmful practices and improve young children's diets. Nutrition Reviews, 2020:78(10), 866-883.
13. Meller, W., Burns, L. H., Crow, S., & Grambsch, P. Major depression in unexplained infertility. Journal of Psychosomatic Obstetrics & Gynecology, 2002:23(1), 27-30.
14. Sulyman, D., & Kuranga, A.T. (2022). Depression among women with infertility versus pregnant women at General Hospital Ilorin: A comparative analytical study. Res. J. Health Sci. Vol 10(3).
15. Yangın, H., Kukulu, K., Gulşen, S., Aktaş, M., & Sever, B. A survey on the correlation between

sexual satisfaction and depressive symptoms during infertility. Health Care for Women International, 2016:37(10), 1082-1095.
16. Göker, A., Yanikkerem, E., Birge, O., & Kuscu, N. K. Quality of life in Turkish infertile couples and related factors. Human Fertility, 2018:21(3), 195-203.
17. Erdemoğlu, Ç., & Aksoy Derya, Y. The effect of hypnofertility on fertility preparedness, stress, and coping with stress in women having in vitro fertilization: A randomized controlled trial. Journal of Reproductive and Infant Psychology, 2022:42(4), 569-580.
18. Fata, S., & Tokat, M. A. Does hypnofertility-based nursing care affect cortisol levels, fertility preparedness, and pregnancy outcomes in women undergoing in vitro fertilization? A randomized controlled trial. Biological Research for Nursing, 2021:23(3), 418-429.
19. Dadhwal, V., Choudhary, V., Perumal, V., & Bhattacharya, D. Depression, anxiety, quality of life and coping in women with infertility: A cross-sectional study from India. International Journal of Gynecology & Obstetrics, 2022:158(3), 671-678.
20. Xu, H., Ouyang, N., Li, R., Tuo, P., Mai, M., & Wang, W. The effects of anxiety and depression on in vitro fertilisation outcomes of infertile Chinese women. Psychology, Health and Medicine, 2017:22(1), 37–43.
21. Fassino S, Pierò A, Boggio S, Piccioni V, Garzaro L. Anxiety, depression and anger suppression in infertile couples: a controlled study. Hum Reprod. 2002:17:2986–94.
22. Sis Çelik, A., & Kırca, N. Primer infertil kadınların infertiliteye bağlı yaşadıkları stres düzeyleri ve etkileyen bazı faktörlerin belirlenmesi. Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi, 2018:21(2), 104-114.
23. Kutlu, L., & Varışoğlu, Y. İnfertilite tedavisi olan kadınların psikolojik ihtiyaçları ile yardım arama tutumları arasındaki ilişki. BANÜ Sağlık Bilimleri ve Araştırmaları Dergisi, 2021:3(2), 72-85.
24. Taşkın, M., Usta, A., Cüce, C., Adalı, E., & Arslan, M. İnfertil kadınlarda anksiyete, depresyon ve ilişkili faktörler. European Journal of Health Sciences, 2016:2(3), 79-84.
25. Kamışlı, S., Terzioğlu, C., & Bozdağ, G. İnfertil kadınların ruhsal durumları: Umutsuzluk, anksiyete ve depresyon düzeyleri. J Psychiatric Nurs, 2021:12(1), 43-49.
26. Shahraki, Z., Ghajarzadeh, M., & Ganjali, M. Depression, anxiety, quality of life and sexual dysfunction in Zabol women with infertility. Mædica, 2019:14(2), 131-134.

Osmangazi Journal of Med, 2025;47(1): 110-127
DOI: 10.20515/otd.1537723

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

An Original Genetic Protocol for the Investigation of Y Microdeletions in Male Infertile Patients

Özgün Bir Genetik Protokol ile Erkek İnfertil Hastalarda Y Mikrodelesyonlarının İncelenmesi

[1]Aysen Akhundova, [2]Sezin Canbek, [3]Burcu Turkgenç

[1] Uskudar University, Institute of Natural and Applied Sciences, Department of Molecular Biology, Istanbul, Türkiye
[2] Health Sciences University, Umraniye Training and Research Hospital, Department of Medical Genetics, Istanbul, Tükiye
[3]Uskudar University, Faculty of Medicine, Department of Basic Medical Sciences, Department of Medical Biology, Istanbul, Türkiye

ORCID ID of the authors
AA. 0009-0007-8003-4049
SC. 0000-0001-9516-0047
BT. 0000-0001-7306-5866

Correspondence / Sorumlu yazar:
Burcu TÜRKGENÇ

Uskudar University, Faculty of Medicine, Department of Basic Medical Sciences, Department of Medical Biology, Istanbul, Türkiye

e-mail: burcu.turkgenc@uskudar.edu.tr

Abstract: The inability to conceive during 12 months or more of consistent, unprotected vaginal sex is known as infertility. In 30% of patients diagnosed with male infertility due to oligozoospermia and azoospermia, infertility is related to genetic causes. Y chromosome microdeletions (YMCs) are seen in idiopathic azoospermia (15-20%) and idiopathic oligozoospermia (7-10%). Complete or partial deletion status affects the patient's production of viable sperm. In this study we aimed to investigate partial and complete Y microdeletions in male infertile patients with a unique genetic protocol, taking into account the recommendations of the EAA/EMQN 2023 guidelines. In this study, DNA materials from 45 patients, most of whom had azoospermia, 1 healthy female, and 1 healthy male control DNA were analyzed for Y chromosome AZF complete and partial microdeletions using the gold standard two-step multiplex PCR methodology, and data from 45 patients were compared with results from another commercial kit. In our study, the Y microdeletion rate was 11.1% in 45 male patients diagnosed with male infertility. Of a total of 5 patients with deletions, 2 (Patients 21 and 31) had partial AZFb+c (40%) with loss of the Y chromosome terminal heterochromatin region (Sy160), 1 (Patient 23) had complete AZFc (20%) with preservation of the Y chromosome terminal heterochromatin region (Sy160), and 2 (Patients 25 and 35) had complete AZFa+b+c (40%) microdeletions. ZFY/ZFX and SRY (sY14) were preserved in Patients 25 and Patient 35 with complete AZFa+b+c deletions. The karyotype analysis result of Patient 35 was 46, XX male. A unique genetic protocol, based on the current 2023 EAA/EMQN guidelines, has been developed to examine Y microdeletions in male infertile patients with high sensitivity and accuracy and provides advantages over many previous protocols.
Keywords: Azoospermia, AZF, male infertility, Y chromosome microdeletion, multiplex PCR

Özet: Düzenli, korunmasız vajinal cinsel ilişkiden 12 ay veya daha uzun süre sonra gebe kalamama, infertilite olarak bilinmektedir. Oligozospermi ve azospermiye bağlı erkek infertilitesi tanılı hastaların %30'unda infertilite, genetik nedenlerle ilişkilidir. İdiyopatik azospermide (%15-20) ve idiyopatik oligozoospermide (%7-10), Y kromozom mikrodelesyonları görülmektedir. Komple veya parsiyel delesyon durumu, hastanın canlı sperm üretimini etkilemektedir. Çalışmamızda, EAA/EMQN 2023 klavuzu önerileri dikkate alınarak, özgün bir genetik protokol ile erkek infertil hastalarda parsiyel ve komple Y mikrodelesyonlarının incelenmesi amaçlandı. Çalışmada çoğu azospermili, 45 hastaya ait DNA materyali, 1 sağlıklı kadın ve 1 sağlıklı erkek kontrol DNA'sı, Y kromozomu AZF komple ve parsiyel mikrodelesyon tayinini gerçekleştirmek üzere, altın standart olarak görülen iki aşamalı multipleks PZR metodolojisini kullanıldı ve 45 hastanın verileri, diğer bir ticari kitle elde edilen sonuçlarla karşılaştırıldı. Çalışmamızda erkek infertilitesi tanısı almış 45 erkek hastada Y mikrodelesyon oranı %11,1 olarak belirlenmiştir. Delesyon belirlenen toplam 5 hastanın 2'sinde (Hasta 21 ve 31), Y kromozomu terminal heterokromatin bölgenin (Sy160) de kaybıyla eşlik eden parsiyel AZFb+c (%40), 1'inde (Hasta 23) Y kromozomu terminal heterokromatin bölgenin (Sy160) korunduğu komple AZFc (%20), 2 hastada (Hasta 25 ve 35) ise komple AZFa+b+c (%40) mikrodelesyonu saptanmıştır. Komple AZFa+b+c delesyonları saptanan Hasta 25 ve Hasta 35'de ZFY/ZFX ve SRY (sY14) pozitif olarak değerlendirilmiştir. Hasta 35'in karyotip analiz sonucu 46,XX erkek olarak tespit edilmiştir. Güncel 2023 EAA/EMQN kılavuzları dikkate alınarak geliştirdiğimiz benzersiz genetik protokol ile, erkek infertil hastalarda, Y mikrodelesyonlarının yüksek hassasiyet ve doğrulukla incelenmesi sağlanmıştır ve önceki çoğu protokolelere göre avantajlar sağlamaktadır. AZF komple ve parsiyel delesyonların tanısı prognostik öneme sahiptir ve hastanın tedavi seçeneklerini büyük oranda etkiler.
Anahtar Kelimeler: Azospermi, AZF, erkek infertilitesi, Y kromozom mikrodelesyon, multipleks PZR.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Uskudar University (Decision no: 20244/96-1, Date: 29.01.2024).

Informed Consent: The authors declared that informed consent form was signed by the patient.

Authorship Contributions: All authors contributed equally to the study.

Copyright Transfer Form: Copyright Transfer Formwas signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Received 27.08.2024

Accepted : 03.01.2025

Published : 04.01.2025

How to cite/ Atıf için: Akhundova A, Canbek S, Turkgenc B, An Original Genetic Protocol for the Investigation of Y Microdeletions in Male Infertile Patients, Osmangazi Journal of Medicine, 2025;47(1):110-127

1. Introduction

Infertility has always been the main problem of reproductive medicine. According to the World Health Organization (WHO), infertility is a specific disease state and should be considered a public disease due to its prevalence (1,2). The absence of conception after regular, unprotected sexual activity for a minimum of a year is known as infertility (3). The causes of infertility are wide-ranging and still not fully understood; in approximately 30% of infertile couples, no cause can be identified (called idiopathic infertility). Infertility is influenced by many biological factors, making it highly complex and heterogeneous. Therefore, it is controversial whether infertility is a disease, a condition, or a symptom (4).

The male factor accounts for 40-60% of infertility. Male infertility can present with a variety of semen phenotypes including qualitative defects associated with sperm cells, including azoospermia (complete absence of spermatozoa in the ejaculate), oligozoospermia (reduced number of spermatozoa), necrozoospermia (presence of dead sperm) and reduced sperm. These anomalies can be caused by various factors including other health complications (e.g. varicocele, cystic fibrosis, and obesity), infections, lifestyle choices, and environmental and genetic factors (4).

Y chromosome microdeletions (YCM) represent the absence of DNA segment(s) or gene(s) from the functionally active portion of the Y chromosome (5). Y chromosomal microdeletions are considered to be the most common structural chromosomal abnormality associated with failure of sperm production, with an overall prevalence of 1% to 58%, specifically 15-20% in idiopathic azoospermic men and 7-10% in idiopathic oligozoospermic men, and 2-3% of ICSI candidates are microdeletion carriers (6). The frequency of Y microdeletion was reported to be 9.6% in azoospermic and oligozoospermic infertile Turkish men (7).

In addition to the factors controlling testicular differentiation and maturation, a third genetic factor or gene cluster located on the Y chromosome in the distal part of the long arm (q) of the Y chromosome (Yq11) and controlling spermatogenesis is called azoospermia factor (5). Detailed molecular analyses have divided the azoospermia factor into three subregions AZFa, AZFb, and AZFc (8). Although the AZFd region has been proposed as the fourth region (9), it is known that the AZFd region does not exist in the current literature (10). Partial or complete deletion of AZF regions disrupts spermatogenesis. Since the Y chromosome sequence was mapped in 2003, microdeletions have been categorized based on the palindromic structure of euchromatin, which is made up of amplicons, which are repeat units (11). Several clinically relevant microdeletion patterns have been defined at the AZF locus including AZFa, P5-proximal P1 (AZFb), P5-distalP1 (AZFbc), P4-distal P1 (AZFbc), and b2/b4 (AZFc) (12). Deletions are caused by intrachromosomal recombinations between homologous sequences (11). The most common complete deletion type in the literature is AZFc deletion (70-80%), followed by AZFa (0.5-9%), AZFb (1-7%) and AZFbc (1-20%) (10). It has been reported that deletions detected as AZFabc are most probably associated with an abnormal karyotype such as 46,XX male, or iso(Y) (13). The frequency of Y microdeletions in infertile male patients with mosaic karyotype was reported as high as 71.43% (14). It was documented that AZFa and AZFb microdeletions were found in four (28.6%) of 14 patients with Klinefelter syndrome, and screening for Y microdeletions should be part of the diagnostic workup for those patients, especially in those under consideration for assisted reproductive techniques (15). In a recent study, it was emphasized that it is very important to perform a routine chromosomal karyotype analysis in patients presenting with male infertility along with an examination for YMCs (16).

The diagnosis of AZF deletions has prognostic importance and greatly affects the treatment options of the patient. Depending on whether the deletion is complete or partial, the sperm production of the patient may be variable and the success of benefiting from assisted reproductive techniques may be affected. Testicular sperm extraction (TESE) or (ICSI) applications are not recommended in patients with complete AZFa or AZFb deletion because there is no sperm in the ejaculate (17,18). In contrast, live sperm can be found in case of partial deletion (18–20). In case of partial AZFa and AZFb and complete AZFc deletion, a successful TESE or ISCI procedure can be performed (10). The importance of partial AZFc deletions in terms of assisted reproductive techniques is controversial (21). The cost of treatment options for infertile male patients is high. Therefore, chromosome analysis and YMC tests should be performed in infertile male patients before assisted reproductive techniques are implemented (22).

Although various methodologies have been implemented in the literature to determine AZF deletion, the gold standard protocol currently used in the genetic diagnosis of the disease is Multiplex Polymerase Chain Reaction (PCR). Even though there are many diagnostic tests and genetic protocols in the current literature, technical limitations and analysis restrictions of the methodologies have been explained in detail in the EAA/EMQN 2023 guidelines (10). Therefore, it is crucial to differentiate complete and partial AZFa, b, and c deletions with a low-cost genetic protocol with high sensitivity and specificity. In accordance with the new recommendations of the EAA/EMQN 2023 guideline, Sequence-Tagged-Site (STS) primers recommended to be used in Y microdeletion studies for accurate and sensitive discrimination of AZFabc complete and partial deletions have attracted attention.

Therefore, based on the new recommendations in the EAA/EMQN 2023 guidelines and a comprehensive literature review, we have established a new protocol for the diagnosis of Y microdeletion that will be superior to the current protocols used in Y microdeletion diagnosis and cost-effective compared to the competitors of real time PCR or fragment analysis in the market. The study aims to create a unique genetic protocol that can be determined by a simple PCR device and agarose gel electrophoresis protocol available in every genetic laboratory, can be easily applied, will be preferred for use in Turkey and the international market, and is superior to its local competitors in terms of the number of regions and scope compared to its competitors. At the same time, the study aims to ensure that patients benefit from assisted reproductive techniques in the most effective way by combining genetic data with clinical data and to create a road map for future studies.

2. Materials and Methods

Collection of Patient Materials

DNA material belonging to 45 patients diagnosed with male infertility who previously applied to the Genetic Diagnosis Centre of Ümraniye Training and Research Hospital, 1 healthy female and 1 healthy male control DNA were used. Ethics committee approval of our study was obtained by the Üsküdar University Non-Interventional Research Ethics Committee No: 61351342/ OCAK 2024-96). YMC analysis of the DNA material previously obtained from the patients included in the study was performed at the Medical Genetics Laboratory of Üsküdar University Faculty of Medicine. Patients between 20-60 years of age, male individuals with at least 1 sperm parameter abnormality, and patients whose karyotype chromosome analysis resulted in normal (46,XY) or sex chromosome abnormality (47,XXY, 47,XYY... etc.) were included in the study within the scope of inclusion criteria. Individuals under 20 years of age and over 60 years of age, patients with semen infection, and patients diagnosed with infertility as a result of another hereditary disease (congenital adrenal hyperplasia, cystic fibrosis, primary ciliary dyskinesia, Kalmann syndrome, Prader Willi syndrome, sickle cell anemia, etc.) other than sex chromosome anomalies were excluded from the study. 1 healthy male control (20-60 years of age, no infertility diagnosis, no suspicion of a sex-related disease, normal karyotype analysis) and 1 healthy female control (20-60 years of age, no suspicion of a sex-related disease, normal karyotype analysis) were used in the study. Study subjects underwent Y microdeletion testing with one of the routinely used and validated commercial kits for subsequent protocol comparison.

Optimization of the Y Microdeletion Analysis Genetic Protocol

A genetic protocol for complete and partial AZF a, b, and c deletions on the Y chromosome was established from DNA samples. A 2-step YMC genetic protocol was optimized by using 45 infertile male infertile patient DNA, 1 healthy female control DNA, and 1 healthy male control DNA. All DNA materials were sent from Umraniye Training and Research Hospital, and the accuracy, sensitivity, and specificity of the protocol were ensured. In the genetic protocol we developed, we identified and orderedSTS primer pairs located at specific intervals on the Y chromosome, taking into account a comprehensive literature review and the recommendations of the EAA/EMQN 2023 Y microdeletion guideline. We accessed the STS primer sequences with the help of MSY Breakpoint Mapper (http://breakpointmapper.wi.mit.edu/mapper.html) and EAA/EMQN 2023 guideline (10). We checked the accuracy of the forward and reverse primer sequences via the UCSC In-Silico PCR website (https://genome.ucsc.edu/cgi-bin/hgPcr). A comprehensive list of all primer pairs (30 pairs) planned to be used in the first and second-step PCR steps, along with primer sequences, chromosome

locations, and PCR product sizes is presented in Table 1.

Table 1. STSprimer pairs used in the Y microdeletion study and their locations on the Y chromosome (Human GRCh38/hg38)

Primer Name	PCR Step	Region	Location	Size (bp)	Forward sequence	Reverse sequence
ZFY /ZFX	**First Step**	**p arm**	**Y:2978942- 2979436**	**495**	**ACCRCTGTACTGACTGTGATTACAC**	**GCACYTCTTTGGTATCYGAGAAAGT**
SRY /sY14	**First Step**	**p arm**	**2787066- 2787535**	**472**	**GAATATTCCCGCTCTCCGGA**	**GCTGGTGCTCCATTCTTGAG**
sY81	**First Step**	**AZFa**	**11975704- 11975912**	**209**	**AGGCACTGGTCAGAATGAAG**	**AATGGAAAATACAGCTCCCC**
sY82	Second Step	AZFa	12207374- 12207637	264	ATCCTGCCCTTCTGAATCTC	CAGTGTCCACTGATGGATGA
sY1064	Second Step	AZFa	12321376- 12321485	110	GGGTCGGTGCACCTAAATAA	TGCACTAAAGAGTGATAATAAATTCTG
sY86	**First Step**	**AZFa**	**12495697- 12496014**	**320**	**GTGACACACAGACTATGCTTC**	**ACACACAGA GGG ACAACCCT**
sY84	**First Step**	**AZFa**	**12678105- 12678432**	**328**	**AGAAGGGTCCTGAAAGCAGGT**	**GCCTACTACCTGGAGGCTTC**
sY1065	Second Step	AZFa	13110497- 13110735	239	TCAGGTACTGTGATGCCGTT	TGAAGAGGACACAAAGGGAAA
sY88	Second Step	AZFa	13492084- 13492206	123	TTGTAATCCAAATACATGGGC	TGCACTAAAGAGTGATAATAAATTCTG
sY182	**First Step**	**AZFa**	**13868910- 13869034**	**125**	**TCAGAAGTGAAACCCTGTATG**	**GCATGTGACTCAAAGTATAAGC**
sY105	Second Step	AZFb	17245408- 17245708	301	AAGGGCTTCTTCTCTTGCTT	AGGGAGCTTAAACTCACCGT
sY108	Second Step	AZFb	17510991- 17511350 18394662- 18395021	360	TTGTGGATTGTTGTTTTTGTTG	AAGACAATGTTGTACCGGCA
sY1224	Second Step	AZFb	18449739- 18450378	640	GGCTTAAACTTGGGAGGGTG	CAAAGAGCCTCCCAGACCA
sY117	**First Step**	**AZFb**	**18549981- 18550242 18770164- 18770425**	**262**	**GTTGGTTCCATGCTCCATAC**	**CAGGGAGAGAGCCTTTTACC**
sY121	Second Step	AZFb	18890192-18890381	190	AGTTCACAGAATGGAGCCTG	CCTGTGACTCCAGTTTGGTC
sY124	Second Step	AZFb	19974696- 19974804	109	CAGGCAGGACAGCTTAAAAG	ACTGTGGCAAAGTTGCTTTC
sY127	**First Step**	**AZFb**	**20408532- 20408804**	**273**	**GCTCACAA ACG AAAAGAAA**	**CTGCAGGCAGTA ATAAGGGA**
sY130	**First Step**	**AZFb**	**21082005- 21082177**	**173**	**AGAGAGTTTTCTAACAGGGCG**	**TGGGAATCACTTTTGCAACT**
sY134	**First Step**	**AZFb**	**21394175- 21394477**	**301**	**GTCTGCCTCACCATAAAACG**	**ACCACTGCCAAAACTTTCAA**
sY1258	Second Step	AZFc	21924767- 21925734	968	AACCCCATCTCTAGCAAAAATATG	TAGGTGACAGGGCAGGATTC
sY1161	Second Step	AZFc	22092892- 22093221 22493184- 22493513	330	CGACACTTTTGGGAAGTTTCA	TTGTGTCCAGTGGTGGCTTA
sY1192	Second Step	AZFc	22726631- 22726885	255	ACTACCATTTCTGGAAGCCG	CTCCCTTGGTTCATGCCATT
sY1191	Second Step	AZFc	22729473- 22729857	385	CCAGACGTTCTACCCTTTCG	GAGCCGAGATCCAGTTACCA
sY153	**First Step**	**AZFb**	**22866498- 22866636**	**139**	**GCATCCTCATTTTATGTCCA**	**CAACCCAAAAGCACTGAGTA**
sY255	**First Step**	**AZFb**	**23168670- 23168793 23179510- 23179633 23190358- 23190481 23228061- 23228184**	**124**	**GTTACAGGATTCGGCGTGAT**	**CTCGTCATGTGCAGCCAC**
sY254	**First Step**	**AZFc**	**23170046- 23170425 23180886-23181265 23191734- 23192113 23226429- 23226808**	**380**	**GGGTGTTACCAGAAGGCAAA**	**GAACCGTATCTACCAAAGCAGC**
sY1291	Second Step	AZFc	23358923- 23359449	527	TAAAAGGCAGAACTGCCAGG	GGGAGAAAAGTTCTGCAACG
sY1206	**First Step**	**AZFc**	**25289447- 25289840**	**394**	**ATTGATCTCCTTGGTTCCCC**	**GACATGTGTGGCCAATTTGA**
sY1201	Second Step	AZFc	26311169- 26311845	677	CCGACTTCCACAATGGCT	GGGAGAAAAGTTCTGCAACG
sY160	First Step	Terminal	50000000– 50000235	236	TACGGGTCTCGAATGGAATA	TCATTGCATTCCTTTCCATT

First-Step of PCR

The STS primers used in the first-step of the genetic protocol design were determined by considering the recommendations of the EAA/EMQN 2023 guideline (10). In the multiplex PCR method, ZFX/ZFY and SRY primers were used as internal controls. Because the ZFX/ZFY primer pair shows homology in the short arm of both the X and Y chromosomes. Therefore, this primer pair is expected to amplify in DNA material from both males and females. The SRY primer is another sex-determining marker located on the short (p arm) of the chromosome and is expected to amplify in all male individuals, whether infertile or not. The other primers ordered in our protocol were male-specific and amplified only when male DNA material was used. Three sets of multiplex PCR (sets A, B, and C) were pooled, each containing four to six primer pairs, to identify deletions in the AZFa, b, and c regions. The primers to be used in mix sets A, B, and C in the multiplex PCR method are shown in Table 2. Stock primers (100 pmol/µl) to be used in each of the A, B, and C mix primer sets were pooled using the formula M1 x V1= M2 x V2 with a final concentration of 5 pmol/µl.

Table 2. Primers of Mix Set A, B, and C in the first-step of PCR

A Mix	B Mix	C Mix
SY1206-394 bp	ZFX/ZFY-495 bp	SRY-472 bp
SY86-320 bp	SY254-380 bp	SY134-301 bp
SY117-262 bp	SY84-328 bp	SY160-236 bp
SY130-173 bp	SY127-274 bp	SY255-124 bp
SY182-125 bp	SY81-209 bp	
	SY153-139 bp	

For the fmultiplex PCR reaction, 3 separate A, B, and C Master mixes for primer sets A, B, and C were prepared as shown in Table 3. The table shows the PCR components, the amounts to be collected from each PCR component, and the expected final concentrations. For each master mix, 1 DNA sample from a fertile male, 1 DNA sample from a fertile female, and a DNA-free water control sample were used in the PCR reactions along with the infertile patient samples whose deletion status was questioned. For each A, B, and C master mix, 1 more reaction mix was prepared than the total number of patient and control samples and distributed into PCR tubes at 22.5 µl per reaction. 2.5 µl DNA was added to the reaction mixes .

Table 3. Master mix preparation for primer sets A, B, and C

PCR Components	Amount	Final Concentration
10X Taq Buffer	2,5 µL	1x
dNTP Mix (2.5 mM)	3 µL	0,3 mM
Primer Mix A, B or C (5 pmol/µL)	2 µL	0,4 µM
25 mM MgCl2	2 µL	2 mM
Taq DNA Polymerase (5 U/µL)	0,5 µL	2,5 Unit
Nuclease-free water	12,5 µL	-
Subtotal	22,5 µL	-
Template DNA (~30-50 ng/µL)	2,5 µL	75-125 ng
Total volume	25 µL	

The prepared samples were amplified by a Thermal Cycle Device (Applied Biosystem, Thermo Fisher Scientific, USA). After pre-denaturation at 95°C for 3 minutes, 40 cycles of amplification were performed at 95°C for 30 seconds, 57°C for 40 seconds, 72°C for 45 seconds, and 72°C for 7 minutes for the last elongation step. After PCR, the samples were loaded into the wells of a 3% 100 ml

agarose gel prepared in 1 x TBE buffer containing ethidium bromide at a final concentration of 0.3 µg/mL. After the cap and power cables were replaced, the current was applied from the power supply. PCR products were run for 45 minutes at 100 volts (400 mA) using a horizontal gel electrophoresis system (Bio-Rad, USA). The band positions and presence of PCR products were visualized using a UV Gel Imaging system (Gel Doc XR+ Gel Documentation System, Bio-Rad, USA).

Second Step of PCR

DNA samples in which no deletion was detected in the first-step PCR study were excluded from the second-step PCR analysis and were considered to have no deletion. However, if a deletion was detected in 1 or more of the primers used in the first-step multiplex PCR study, additional primers were used behind and in front of the deletion, region to determine the start and end of the deletion (breakpoints) and to determine whether the deletion was complete or partial.

Following PCR, the samples were visualized by horizontal agarose gel electrophoresis and UV imaging as described in the previous step. Complete or partial deletions in AZFa, b, and c regions were determined by analyzing the results of the second multiplex PCR.

Data Analysis

All patient data studied with the Y microdeletion protocol were evaluated for partial and complete deletions using the current EAA/EMQN guideline (10). Clinical and genetic data were summarized in a table, and the results found in 45 patients were compared and interpreted. The demographic and clinical characteristics of the patients and Y microdeletion genotype results were presented as frequency distributions (n and %), Mean + SD, and Median (min-max) for numerical data.

3. Results

In the study, as a result of Y microdeletion analysis, we tested and compared the results of 1 healthy male and 1 healthy female control individual and the DNA material of a total of 45 individuals who were previously admitted to the Genetic Diagnosis Centre of Umraniye Training and Research Hospital and diagnosed with male infertility. No deletion was detected in 40 patients (88.9%) and 5 (11.1%) of the 45 patients studied. Of the 45 patients, 43 (95.6%) were diagnosed with azoospermia, 1 (2.2%) with oligoasthenoteratospermia, and 1 (2.2%) with asthenoteratospermia (Figure 1). As a result of Physical Examination/Ultrasonography (USG) findings, left-sided stage 1 varicocele was detected in 9 patients (20%). Follicle-stimulating hormone (FSH) was found to be elevated in 5 (Patients 4, 20, 28, 31, 31, and 35), luteinizing hormone (LH) in 5 (Patients 4, 28, 30, 31, and 35) and testosterone (TT) in 1 (Patient 5) of 11 patients. Karyotype examination revealed 47,XXY karyotype (Klinefelter syndrome) in 1 of 40 patients (Patient 28) (2.5%) and 46,XX male syndrome in 1 of 5 patients (Patient 35) (20%). The mean age of the study patients was 34.6±6.8 years. We also compared the Y microdeletion results of our genetic protocol with the results of other commercial kit in Table 4.

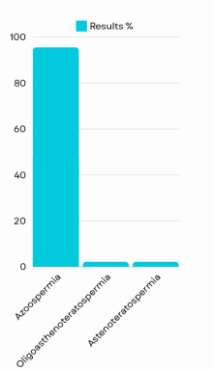


Figure 1. Spermiogram results of 45 patients used in the study. 43 patients (95,6%) were diagnosed with azoospermia, 1 patient (2,2%) with oligoastenoteratospermia, and 1 patient (2,2%) with astenoteratospermia.

Table 4. Examination, laboratory, cytogenetic, and molecular genetic results

Patient No	Age	Spermiogram	Physical Examination /Hormone USG findings	Values	Pathological Diagnosis	Chromosome Analysis	YMD Analysis (Other Commercial Kit*)	YMD* Analysis
1	47	Azoospermia	-	-	Primary infertility	46,XY	Deletion (-)	Deletion (-)

2	60	Azoospermia	-	-	Primary infertility	46,XY	Deletion (-)	Deletion (-)
3	39	Azoospermia	-	-	Primary infertility	46,XY	Deletion (-)	Deletion (-)
4	34	Azoospermia	-	FSH:40.3 LH:33.3 TT:5.11	Primary infertility	46,XY	Deletion (-)	Deletion (-)
5	36	Azoospermia	-	FSH:5.7 LH:3.5 TT:12.88	Primary infertility	46,XY	Deletion (-)	Deletion (-)
6	36	Azoospermia	-	-	Primary infertility	46,XY	Deletion (-)	Deletion (-)
7	35	Oligoasthenoteratospermia	Grade 1 varicocele on the left side	-	-	46,XY	Deletion (-)	Deletion (-)
8	38	Azoospermia	-	-	Primary infertility	46,XY	Deletion (-)	Deletion (-)
9	33	Azoospermia	-	-	-	46,XY	Deletion (-)	Deletion (-)
10	44	Azoospermia	-	-	Primer infertilite	46,XY	Deletion (-)	Deletion (-)
11	30	Azoospermia	-	-	-	46,XY	Deletion (-)	Deletion (-)
12	26	Azoospermia	-	-	Primary infertility	46, XY	Deletion (-)	Deletion (-)
13	38	Azoospermia	-	-	-	46,XY	Deletion (-)	Deletion (-)
14	37	Azoospermia	Grade 1 varicocele on the left side	-	-	46,XY	Deletion (-)	Deletion (-)
15	35	Azoospermia	-	-	Primary infertility	46, XY	Deletion (-)	Deletion (-)
16	31	Azoospermia	-	-	-	46,XY	Deletion (-)	Deletion (-)
17	39	Azoospermia	Grade 1 varicocele on the left side	-	Primary infertility	46,XY	Deletion (-)	Deletion (-)
18	30	Astenoteratospermia	Grade 1 varicocele on the left side	-	-	46,XY	Deletion (-)	Deletion (-)
19	39	Azoospermia	-	FSH:4.8 LH:3.8 TT:4.39	Primary infertility	46,XY	Deletion (-)	Deletion (-)

Table 4. Examination, laboratory, cytogenetic, and molecular genetic results (Continued)

Patient No	**Age**	**Spermiogram**	**Physical Examination /Hormone USG findings Values**	**Pathological Diagnosis**	**Chromosome Analysis**	**YMD Analysis (Other Commercial Kit*)**	**YMD Analysis (Our Genetic protocol)**
20	33	Azoospermia	- FSH:16.1 LH:7.1 TT:5.18	-	46,XY	Deletion (-)	Deletion (-)

21	**45**	**Azoospermia**	**-**	**-**	**Primary infertility**	**46,XY**	**AZFc and AZFd deletion**	**Partial AZFb+c +sY160 deletion**
22	33	Azoospermia	-	-	-	46,XY	Deletion (-)	Deletion (-)
23	**40**	**Azoospermia**	**-**	**-**	**-**	**46, XY**	**AZFc deletion**	**Complete AZFc deletion (sY160+)**
24	33	Azoospermia	Grade 1 varicocele on the left side, a slight decrease in the size of both testicles	FSH:4.75 LH:3.22 TT:3.03	-	46, XY	Deletion (-)	Deletion (-)
25	**32**	**Azoospermia**	**-**	**-**	**-**	**46, XY**	**AZFa+b+c deletion (ZFY/ZFX+, SRY+)**	**Complete AZFa+b+c +sY160 deletion (ZFY/ZFX+, SRY+)**
26	29	Azoospermia	-	FSH:1.6 LH:2.3 TT:2.42	-	46,XY	Deletion (-)	Deletion (-)
27	26	Azoospermia	-	FSH:7.9 LH:7.5 TT:4.09	-	46,XY	Deletion (-)	Deletion (-)
28	26	Azoospermia	-	FSH:21.1 LH:22.5 TT:4.23	Infertility	**47,XXY**	Deletion (-)	Deletion (-)
29	37	Azoospermia	-	-	Primary infertility	46,XY	Deletion (-)	Deletion (-)
30	29	Azoospermia	Grade 1varicocele on the left side	FSH:4.8 LH:8.8 TT:3.72	Primary infertility	46,XY	Deletion (-)	Deletion (-)
31	**34**	**Azoospermia**	**-**	**FSH:31.7 LH:12.1 TT:4.84**	**Infertility**	**46,XY**	**AZFc and AZFd deletion**	**Partial AZFb+c +sY160 deletion**
32	30	Azoospermia	Grade 1 varicocele on the left side	-	-	46,XY	Deletion (-)	Deletion (-)
33	33	Azoospermia	Grade 1 varicocele on the left side	-	-	46,XY	Deletion (-)	Deletion (-)

Table 4. Examination, laboratory, cytogenetic, and molecular genetic results (Continued)

Patient No	**Age**	**Spermiogram**	**Physical Examination USG findings**	**/Hormone Values**	**Pathological Diagnosis**	**Chromosome Analysis**	**YMD Analysis (Other Commercial Kit*)**	**YMD Analysis (Our Genetic protocol)**
34	33	Azoospermia	Grade 1 varicocele on the left side	FSH:8.5 LH:4.1 TT:3.3	-	46,XY	Deletion (-)	Deletion (-)
35	**30**	**Azoospermia**	**-**	**FSH:48 LH:29.2 TT:2.66**	**-**	**46, XX**	**AZFa+b+c deletion (ZFY/ZFX+, SRY+)**	**Deletion (+) Complete AZFa+b+c +sY160 deletion (ZFY/ZFX+, SRY+)**
36	30	Azoospermia	-	-	Primary infertility	46,XY	Deletion (-)	Deletion (-)
37	33	Azoospermia	-	FSH:5 LH:5.6 TT:3.08	-	46,XY	Deletion (-)	Deletion (-)
38	32	Azoospermia	-	FSH:6.3 LH:2.85 TT:2.85	-	46,XY	Deletion (-)	Deletion (-)

39	27	Azoospermia	-	-	-	46,XY	Deletion (-)	Deletion (-)	
40	20	Azoospermia	-	-	-	46,XY	Deletion (-)	Deletion (-)	
41	46	Azoospermia	-	-	Primary infertility	46,XY	Deletion (-)	Deletion (-)	
42	35	Azoospermia	-	-	-	46,XY	Deletion (-)	Deletion (-)	
43	42	Azoospermia	-	-	Primary infertility	46,XY	Deletion (-)	Deletion (-)	
44	33	Azoospermia	-	-	Primary infertility	46,XY	Deletion (-)	Deletion (-)	
45	28	Azoospermia	-	-	-	46,XY	Deletion (-)	Deletion (-)	

*Abbreviations; AZF: Azoospermia Factors, FSH: Follicle stimulating hormone, LH: Luteinising hormone, TT: Testosterone, USG: Ultrasonography, YMD: Y microdeletion. Normal values; FSH: 1.5-12.4 mlU/mL, LH: 1.8-8.6 mIU/mL, Testosterone: 3-10 ng/mL. *****For some ethical and legal constraints, the manufacturer's name of the commercial kit used in the study is not shared in our current publication.*

In our study, sY1206 (394 bp), sY86 (320 bp), sY117 (262 bp), sY130 (173 bp), sY182 (125 bp) for Mix A, ZFY/ZFX (495 bp), sY254 (380 bp) for Mix B, sY84 (328 bp), sY127 (274 bp), sY81 (209 bp), sY153 (139 bp), SRY(sY14) (472 bp), sY134 (301 bp), sY160 (236 bp), sY255 (124 bp) primers were used for C Mix. Figure 2 shows agarose gel images of the first-step PCRs of reaction mixtures A, B, and C of Patients studied from 21 to 36. Patients 21 and 31 had deletions in sY1206 in Mix A, sY153, and sY254 in Mix B, and sY255 and sY160 in Mix C. According to the results, the deleted primer regions in Patients 21 and 31 belonged to the AZFc region. The heterochromatin region of the Y chromosome (sY160 primer) was not amplified in either patient, suggesting that the chromosome's terminal end had been deleted. In patient 23, a deletion suggestive of AZFc deletion was detected with loss of sY1206 in Mix A, sY153, and sY254 in Mix B, and sY255 in Mix C. However, unlike the previous two patients, the heterochromatin region of the Y chromosome (Sy160) was present in Patient 23 (Figure 2, C Mix). In Patient 25 and Patient 35, deletions were found in all primers in Mix A, all primers except ZFY/ZFX primer in Mix B, and in all primer regions except SRY (sY14) primer in Mix C suggesting complete AZFa+b+c deletion.

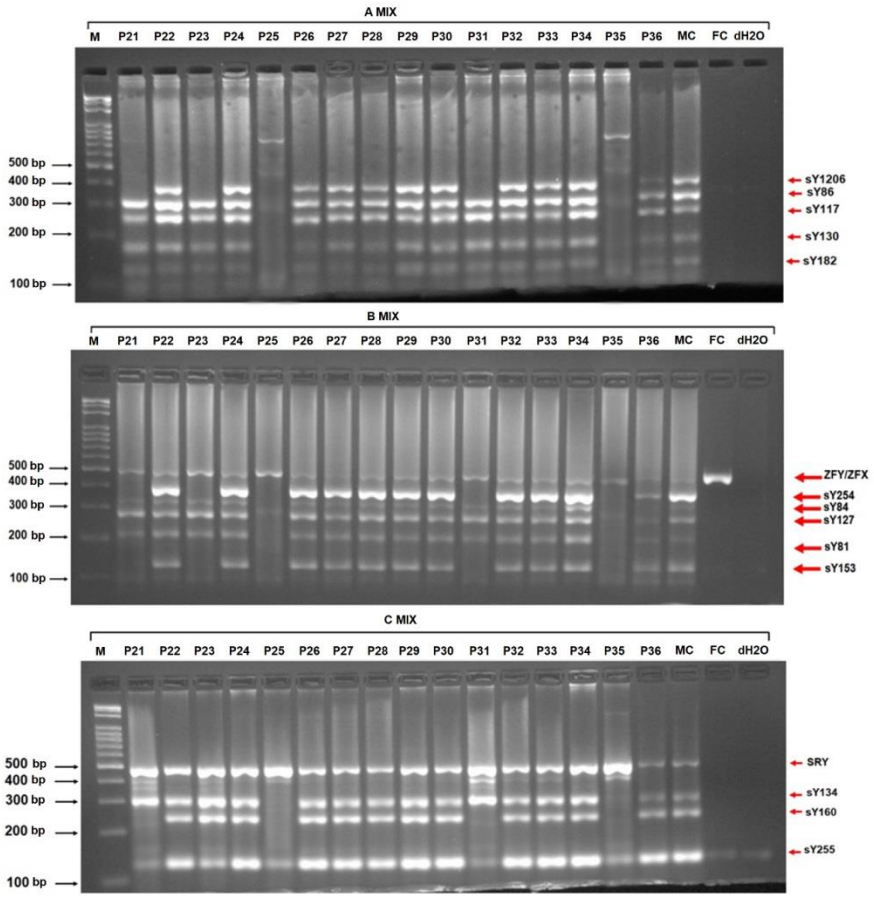


Figure 2. Agarose gel images of A, B, and C mixes of Patient 21 through Patient 36. The black arrow indicates the band positions of DNA Markers (M), while the red arrow indicates the band positions of PCR products with STS primers. M - DNA Marker (1 kb), MC - Male control, FC - Female control, dH2O - DNA-free water control.

In the C-mix in Figure 2, the sY255 primer band is quite bright in patients without deletion and weak in patients with deletion. This is because the sY255 primer band with a product length of 124 bp and the primer dimers that do not bind in the reaction are observed in the same alignment. The primer dimer structures in the female control and DNA-free water control samples also support this conclusion. However, to be sure, the presence of the sY255 deletion in Patients 21, 23, 25, and 31 was confirmed by a second PCR. As shown in Figure 3A, the sY255 primer region was deleted in Patients 21, 23, 25, and 31, except for the fertile male control. The Sy134 primer was used as an internal control primer, which is expected to be present in patients other than Patient 25 with complete deletions, obtained in the first-step of PCR. Sy1161 primer is another primer region that is expected to be present in Patients 21, 23, and 31. According to the results, the sY1161 primer region was consistent with a deletion in Patients 21 and 31, while it was present in Patient 23 (Figure 3A).

In the first-step PCR, in Patients 21, 23, and 31, all primer regions from the p arm of the Y chromosome to sY134 in the q arm AZFb region of the Y chromosome were present, and a deletion including sY153 in the AZFc region was detected. Therefore, to determine the breakpoints of deletions and to differentiate complete/partial deletions, we performed second-step PCR in 3 samples using primer pairs sY1258, sY1161, sY1192, sY1191, sY1161, sY1192, sY1191 between sY134 primer and sY153. The result of the second-step PCR for sY1258 primer in Patients 21, 23, and 31 is shown in Figure 3B. sY134 primer was used as an internal control primer in all patients with expected positivity. Fertile male control and DNA-free water control were also included in the study. As seen in Figure 3B, in Patients 21 and 31, the sY1258 region was found to be deleted, but in Patient 23, the sY1258 region was present.

Figure 3C shows the results of the second-step PCR performed with sY1161, sY1192, and sY1191 primer pairs in Patients 21, 23, and 31. In the same

study, sY153 primer was also used as a deletion control in the relevant patients. Fertile male control and DNA-free water control were also included in the study. As seen in Figure 3C, deletions were detected for all primers in Patients 21 and 31, while in Patient 23 the sY1161 primer was present and there were deletions in the sY1192, sY1191, and Sy153 primers.

Finally, since the terminal heterochromatin region of the q arm of the Y chromosome (sY160) was present in Patient 23 in the first-step PCR, but the Sy1206 primer in front of it was deleted, we performed a further second-step PCR with the sY1201 primer between both primers. Since the terminal region (Sy160) was already deleted in Patients 21 and 23, we expected that the sY1201 primer region would also be deleted. For sY1201, we employed both patients as deletion controls. We also used the sY134 primer as an internal control primer that we expected to detect in every patient (Figure 3D). Even though nonspecific bands are present in the figure, the sY1201 region was found to be deleted in Patients 21, 23, and 31.

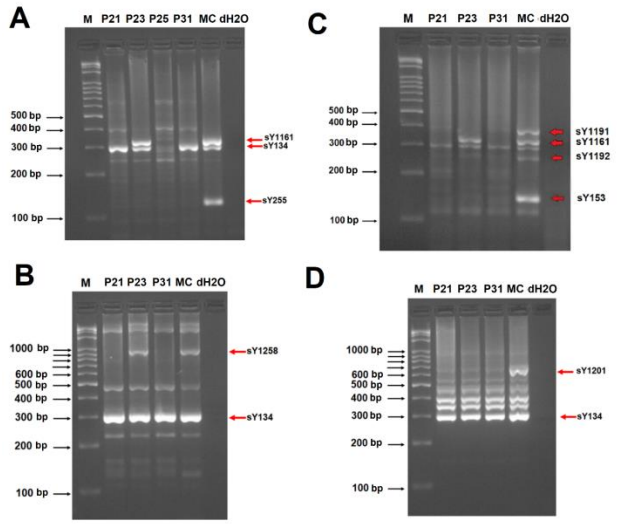


Figure 3. Gel images of the second-step PCR of Patients 21, 23, 25, and 31 with deletion. The black arrow indicates DNA Marker (M) band positions and the red arrow indicates the band positions of PCR products made with STS primers. M - DNA Marker (1 kb), MC - Male, control, dH2O - DNA-free water control. **A.** Confirmation of the presence of sY255 deletion in Patients 21, 23, 25, and 31 by the second study. **B.** Results of the second-step PCR to detect the presence of the sY1258 primer region in Patients 21, 23, and 31. **C.** Second-step PCR result for the detection of sY1161, sY1192, and sY1191 primer regions in Patients 21, 23, and 31. **D.** Second-step PCR result for the detection of the presence of sY1201 primer region in Patients 21, 23, and 31.

Figure 4 shows the results of our Y microdeletion protocol, which was optimized and tested for specificity and reliability, in 45 infertile male patients. The primers used in the first-step are circled in red. The presence of deletion in the primer region studied for the patients is indicated by the '-' symbol, and the absence of deletion is indicated by the '+' symbol. As seen in Figure 4, a deletion starting from sY1258 and including the sY160 heterochromatin terminal region was detected in Patients 21 and 31. In Patient 23, a deletion was detected starting from sY1192 and including sY1201, but the terminal heterochromatin region (sY160) was preserved. In Patients 25 and 35, ZFY/ZFX and SRY regions were intact, while other primer regions were deleted.

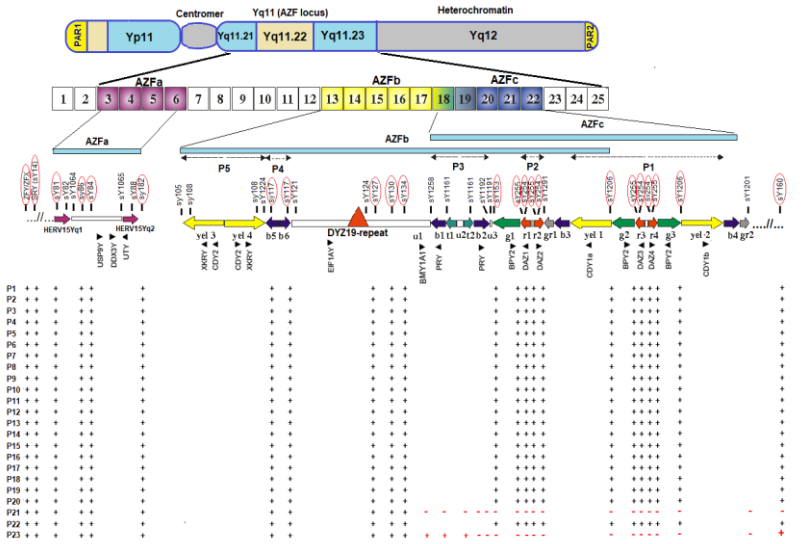


Figure 4. Results of primers used for first and second-step PCR on 45 patients studied.

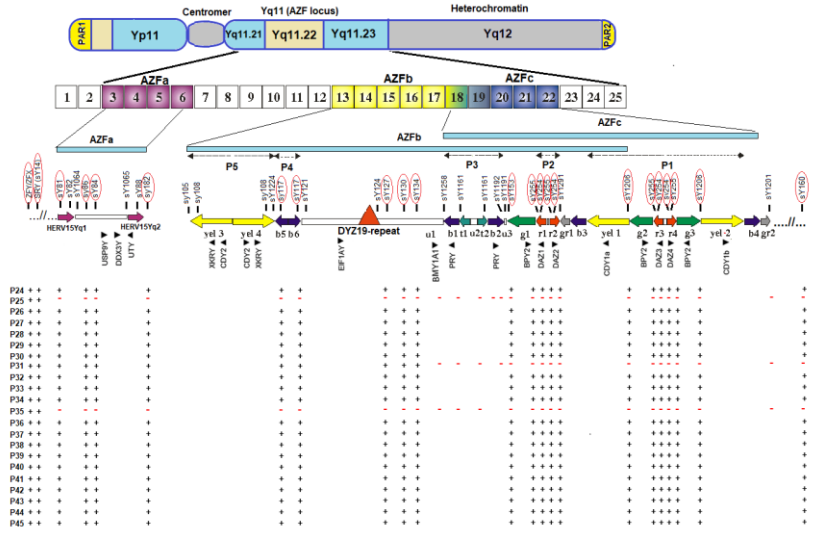


Figure 4. Results of primers used for first and second-step PCR on 45 patients studied (continued).

4. Discussion and Conclusion

Infertility, which is defined as the failure to achieve pregnancy following 1 year of consistent and unprotected vaginal intercourse, is an extremely emotionally, physically, and financially stressful condition for patients (2). For a man to be fertile, he must have appropriate spermatogenesis, successful epididymal maturation and sperm storage, and timely sexual activity. Men are responsible for approximately 20% of infertility cases (23), and an estimated 15–30% of male-related causes are assumed to be genetic (12). The most common genetic causes are YMCs and sex chromosome abnormalities (24). YMCs are the second most common inherited cause of male infertility after Klinefelter syndrome (25).

The diagnosis of AZF deletions has prognostic significance and greatly influences the patient's treatment options. Testicular sperm extraction (TESE) or (ICSI) applications for sperm in the ejaculate of patients with complete AZFa or AZFb deletion are not recommended (18–20), however viable sperm can be found in cases of partial deletion. In cases of partial AZFa and AZFb and complete AZFc deletion, a successful TESE or ISCI

procedure can be performed (10). The importance of partial AZFc deletions in terms of assisted reproductive techniques is controversial (21). The cost of treatment options for infertile male patients is quite high. Therefore, karyotype analysis and YMC tests should be performed before assisted reproductive techniques for these patients (22). Considering the recommendations of the EAA/EMQN 2023 guideline, it was noted that they were insufficient or limited in detecting AZFa, AZFb, and AZFc partial deletions, especially in terms of regional coverage (10).

In the literature, although different methodologies are applied to detect AZF deletions, the gold standard protocol currently used in the genetic diagnosis of the disease is the multiplex PCR methodology. In line with the new recommendations of the EAA/EMQN 2023 guideline (10), 2-step PCR is recommended for the efficient determination of deletions occurring in AZFa, b, and c in Y microdeletion analysis. In the first-step of PCR, six primer regions should be analyzed (sY84, sY86, sY127, sY134, sY254, and sY255). In the manual, it is stated that if one of the primers does not work, the reaction should be repeated. Because there may be a problem due to PCR conditions. If deletions were detected in 2 or more of these primers, it was recommended to proceed to second-step of PCR and determine the breakpoint of the deletion. In our study, we ordered a total of 30 primer pairs containing SRY, ZFX/ZFY, AZFa, b, c, and Y distal heterochromatin regions, taking into account the recommendations of the EAA/EMQN 2023 guideline. By utilizing as many STS markers as possible, the risk of false negative results was decreased and deletion sites were more accurately and highly sensitively identified.

Most of the commercial kits currently widely used in our country are foreign-dependent. Some local Y microdeletion kits developed in our country were also found. Some of these kits work with fragment analysis and some with real-time PCR methodology. Fragment analysis is a high-sensitivity genetic analysis technique that involves fluorescently labeling DNA fragments, capillary electrophoresis, comparison with an internal standard, and size-based differentiation (26). Although fragment analysis is a sensitive methodology compared to multiplex PCR due to the need for fluorescently labeled primers and capillary electrophoresis like ABI, which requires expensive equipment, the reaction cost is considerably increased, and not all centers have fragment analysis devices. Some Y microdeletion kits readily available in the literature are analyzed with real-time PCR methodology, which is a sensitive method. Real-time PCR is a molecular biology laboratory technique based on PCR. It monitors the amplification of a specific target DNA molecule during PCR (i.e., in real time) rather than at the end as in traditional PCR (27). Real-time PCR methodology is costly compared to the requirements of fluorescently labeled probes (TaqMan probes, Scorpion probes, LightCycler probes, etc.) and classical thermal cycling devices. In the literature, methodologies using SYBR GREEN-based real-time PCR methodology instead of high-cost labeled probes are also found. At the beginning of the SYBR Green procedure, double-stranded DNA, primers, and SYBR Green fluorescent dye are added to the reaction mixture. When the primers bind and elongation begins, the SYBR Green dye attaches itself to the double-stranded DNA, initiating fluorescence emission. The amount of fluorescent signal emitted and read by the real time PCR equipment monitor increases with the amplification of DNA (28,29). Since this methodology uses a methodology based on the binding of a fluorescently labeled molecule to double-stranded DNA, its cost is relatively low compared to other probe-based methodologies. However, the cost of SYBR Green-based real-time PCR methodology remains high compared to multiplex PCR. In multiplex PCR, where multiple targets are amplified, it is difficult to distinguish between different amplicons as they all produce the same fluorescent signal. In addition, real-time PCR equipment is not available in every center. When the literature was examined, it was realized that some kits use multiplex PCR methodology. However, in general, when we analyzed the available kits, we found that the majority of these kits were inadequate in detecting AZFa, AZFb, and AZFc partial deletions. In addition, sY83 and sY143 primers, which are included in old kits that are outdated in the literature, are no longer recommended for the determination of deletion breakpoints. For the efficient discrimination of complete and partial AZFa deletions, it is strongly recommended to use sY1064 at the AZFa proximal border instead of sY83, and for the successful identification of AZFb complete and partial deletions, sY143 should no longer be used and sY1192 should be used instead. AZFa proximal border markers sY83 and sY1064 and AZFb distal border markers sY143 and sY1192 cannot be used interchangeably. In addition, the Y chromosome heterochromatin region primer (sY160) is not available in many ready-to-use kit protocols. The

guideline strongly recommends testing the sY160 heterochromatin marker, which also enables the detection of terminal deletions (10).

In our study, 15 pairs of primers were used in multiplex sets in the front panel with first-step PCR. Since the results were expected to be negative in most of the individuals studied (approximately 80–90%), second-step PCR was not required. Out of 45 male patients diagnosed with male infertility, the Y chromosomal microdeletion rate was found in 5 individuals (11.1%) in our study. This result is similar to the literature in Turkey. In a study conducted on 437 infertile male patients in Turkey, it was reported that YMC was found in 44 patients (10.06%) (22). It was observed that the reported frequency of YMCs in infertile male groups varies significantly in the literature according to ethnic origin and geographical location. The prevalence has been reported to be less than 2% in countries such as Germany and Austria, 12% in the United States of America, and 24.2% in Iran (30). This discrepancy may potentially be impacted by the clinical definitions of the patients, the inclusion criteria of the study participants, and incorrect deletion detection.

Partial AZFb+c deletion was found in 2 (4.4%) (Patients 21 and 31), complete AZFa+b+c deletion in 2 (4.4%) (Patient 25 and Patient 35), and complete AZFc deletion in one (2.2%) (Patient 23) of the 45 patients studied. In the literature, in 437 male infertile patients, AZFc partial gr/gr deletion was found in 17 (3.9%), partial AZFb+c in 9 (2.1%), partial AZFc in 8 (1.8%), complete AZFb+c deletion in 4 patients, complete AZFc (0.5%) deletion in 2 (0.5%), and complete AZFa deletion in 1 patient (22). In our study, second-step PCR was not required in individuals with complete AZFa+b+c deletion (Patients 25 and 35). For Patients 21, 23, and 31 with AZFc deletion, second-step PCR analysis was performed by using primer pairs sY1258, sY1161, sY1192, and sY1191 in front of the deletion site to detect the exact breakpoints of the deletions. In the literature, it has been reported that AZFc region deletions are the most common YMC and constitute 60-80% of all reported deletions (10).

In our study, no deletions involving AZFa or AZFb regions alone were detected in any of the patients studied, and there was no need to use the second-step primers ordered for these regions. Therefore, in our novel genetic protocol, most of the cost was incurred by the 3 multiplex set PCRs performed in the first-step. In the literature, it is known that complete deletion of the AZFa region causes ‘Sertoli Cell Only (SCO)’ syndrome, a disease in which germ cells are absent and seminiferous tubules contain only Sertoli cells as a result of loss of *DDX3Y* and *USP9Y* genes (31). AZFa partial deletions are associated with phenotypes ranging from azoospermia to normozoospermia (20). The two STS markers sY84 and sY86 used in the molecular analysis of the AZFa region are located in front of the *USP9Y* and *DDX3Y* genes. According to the pathogenic mechanism of the deletion and available data, when a deletion is detected in both sY84 and sY86, the probability of encountering a complete deletion for AZFa is very high. However, it is possible (although rare) to delete both markers without affecting the two AZFa genes or to affect only *USP9Y* (32,33). Therefore, it is crucial to test deletion breakpoints with additional primers anterior and posterior to AZFa deletions. In AZFa complete deletion, sY82 (present), and sY1064 (absent) are used for the proximal border, and sY1065 (absent), and sY88 (present) are used for the distal border (10). If only sY84 or sY86 are found to be deleted (and amplification failures can be excluded), the AZFa region should be analyzed in more detail (13). However, this event is currently thought to be extraordinarily rare. The average frequency of partial AZFa deletion has been reported to be 5.3% (34). In contrast to our novel genetic protocol, the other studied commercial kit did not include primers sY81, sY82, sY1064, sY1065, and sY88, and was expected to miss partial AZFa deletions if present.

In our study, complete AZFb deletion was not detected. However, partial AZFb+c deletion starting from the P3 palindrome of the AZF region and continuing along AZFc, including the terminal part of the Y chromosome, was found in 2 patients (Patients 21 and 31). In contrast to our novel genetic protocol, other commercial kit results using STS primers sY127, sY130, and sY131 for the AZFb region; sY152 and sY153 for the AZFd region; and sY254 and sY255 for the AZFc region reported AZFc and AZFd deletions in the same 2 patients. In the current literature, sY153 is used as the distal border of the AZFb region and is expected to be present in the presence of AZFb deletion. In addition, sY152 is known to map to DAZ genes, similar to sY255 and sY254, and it has been reported that the “AZFd” region defined upon the suggested absence of sY152 is not present and is not recommended for use (10). In our new genetic protocol, we could also capture partial AZFb deletion by using additional markers sY1258, sY1161, sY1192, and sY1191. Therefore, when the

deletion is detected in the first-step of PCR, it is very important to use additional markers to identify the exact breakpoints of the deletion in a second PCR. In the literature, complete deletions of AZFb have been associated with the meiotic arrest of spermatogenesis and the absence of postmeiotic germ cells. Non-classical partial AZFb deletions occurring in the AZFb region have also been associated with various testicular pathologies, including meiotic arrest, cryptozoospermia, severe oligozoospermia, or oligoasthenoteratozoospermia (OAT syndrome) (35). sY127 and sY134 markers are located in the median and distal parts of the AZFb region. According to available data, in most cases, deletion of both markers indicates complete deletion of the AZFb region. To determine the prognostic value of the deletion in terms of the TESE result, a mandatory deletion elongation analysis with additional markers is required. These are sY105 (present) sY121 and sY1224 (absent) for the proximal border and sY1192 (absent) and sY153 (present) for the distal border. The EAA/EMQN 2023 guideline states that sY1192 has prognostic value for TESE outcomes. Recent data have also shown that sY1224, which was recommended as equivalent to sY121 in previous versions of the guidelines, may still be conserved in a notable number of complete AZFb and AZFbc deletions. Although the phenotypic consequences of this variation have yet to be clarified, the use of both sY121 and sY1224 (in the absence of sY121) is strongly encouraged (10). Similar to complete AZFa deletions, it is almost impossible to obtain sperm by TESE in men with complete AZFb deletions (6,36). It has been reported that TESE may be attempted in azoospermic carriers of atypical AZFb or AZFbc deletions characterized by a proximal breakpoint at the Y chromosome P4 palindrome (instead of P5). Indeed, a smaller deletion with a proximal deletion point at P4 may be associated with the retention of additional AZFb gene copies such as *XKRY*, *CDY2*, and *HSFY* and thus a less severe, TESE-positive outcome (36–38). Similarly, partial AZFb deletions defined by the positivity of the sY1192 distal marker (part of the deletion extension analysis) may also be compatible with residual spermatogenesis. The presence of sY1192 in this patient's deletion model strongly suggests that additional copies of *RMBY1* remain intact, possibly leading to a less severe testicular phenotype (39). Another recent study reached a similar conclusion and emphasized the importance of differentiating between complete (P5/proximal P1) and partial AZFb deletions. Comprehensive analysis of P3 palindrome in the AZF region and overlapping regions of AZFb and AZFc regions is necessary for the clinical evaluation of these patients (40).

In our study, 1 patient (Patient 23) had a result compatible with AZFc complete deletion (b2/b4), including loss of sY1192, sY1191, sY153, sY255, sY254, Sy1291, and sY1206 regions, respectively. However, the heterochromatin terminal region (sY160) was discovered to be preserved in our patient. It is known that the DAZ gene family with a 4-copy polymorphic structure in the r1, r2, r3, and r4 regions in the AZFc region is effective in male germ cell formation and protection (41,42). Deletions occurring in the AZFc region have been associated with sperm maturation defects (43). In complete and partial AZFc deletions, the clinical phenotype may be variable (22). AZFbc deletions occur as a result of intrachromosomal homologous recombination between P5/distal P1 (7.7 Mb) or between P4/distal P1 (7.0 Mb) (44). The two pairs of primers sY254 and sY255 used for the AZFc region are specific for the DAZ gene, located in four copies organized in two clusters on the reference Y chromosome sequence. Based on the available data, deletion of only one of these 2 markers is extremely unlikely and should be considered a technical error. Deletion analysis using the sY160 heterochromatin marker will allow us to understand whether a complete AZFc deletion (b2/b4, sY160 present) is accompanied by a terminal deletion (sY160 absent). Terminal deletions and b2/b4 deletions may be associated with a mosaic karyotype (46,XY/45,X) (45,46), and therefore karyotype analysis is mandatory for these patients for TESE prognostic reasons. In Patient 23, sY160 primer was present, and complete AZFc deletion was not accompanied by the terminal deletion. The other commercial kit we tested did not include the STS primer sY160, which maps to the heterochromatin region of the Y chromosome and missed the deletion of that region. Partial AZFc deletion was not found in our study. However, in our new genetic protocol, there were sufficient additional STS primers (sY1161, sY1191, sY1291, sY1206, and sY1201) to capture partial AZFc deletions. In the literature, sY1291 and sY1191 primers are used for gr/gr partial AZFc deletion (44). The diagnosis is based on the absence of the sY1291 marker and the presence of sY1191. It should be noted that a false deletion rate of 5% was detected in a multicentre study (47), highlighting the importance of optimization of PCR conditions and additional validation steps. The b1/b3 partial deletion is based on the absences of sY1161,

sY1191, and sY1291. The lack of sY1191 identify the b2/b3 partial deletion (48). The other commercial kit we used in the study did not have additional STS primers for the identification of partial AZFc and would have missed partial AZFc deletions anyway.

In our study, ZFY/ZFX and SRY(sY14) primers were included in both the commercial kit and our novel genetic protocol, and regions were present in Patients 25 and 35 with complete AZFa+b+c deletions. The karyotype analysis result of Patient 35 was 46,XX male. In the literature, deletions detected as AZFabc are generally associated with an abnormal karyotype such as 46,XX male, or iso(Y) (10,46). Men with 46,XX karyotype have testicular abnormalities characterized by a genital structure ranging from normal genital structure to ambiguous genitalia. Although pubic hair and penis size are normal during puberty, most individuals with 46,XX testicular disease have gynecomastia, small testicles, and infertility due to azoospermia (49). Individuals with a positive *SRY* gene are followed up after puberty because of small testicles, gynecomastia, azoospermia, and sometimes short stature and atypical genital structures. Gynecomastia is relatively uncommon in these people. In SRY-negative 46,XX male patients, the genitals are more likely to be ambiguous from birth, as in penoscrotal hypospadias and undescended testes. Gynecomastia is common in adolescence if treatment is not received (50).

In conclusion, this study is an important step toward the investigation of Y microdeletions in male infertile patients with a unique genetic protocol. The diagnosis of AZF deletions has prognostic significance and greatly affects the patient's treatment options. Depending on whether the deletion is complete or partial, the sperm production of the patient may be variable, and the success of assisted reproductive techniques may be affected. Chromosome analysis and Y chromosome microdeletion tests should be performed before assisted reproductive techniques are utilized in infertile male patients. The most important technical limitation of our study is the low sample size. Due to the low sample size, the patients with AZFa and AZFb deletions were not detected. However, we believe that the second set of AZFa and AZFb primers we ordered will also work effectively in multiplex PCR sets and discriminate the complete AZFb and complete AZFc. Future studies with larger sample groups and other clinical factors will provide a better understanding of the effects of Y microdeletion on male infertile patients. Such studies will contribute to improving the treatment processes of male infertile patients and developing treatment approaches.

REFERENCES

1. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum Reprod.* 2007;22(6):1506–1512
2. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. *PLOS Med.* 2012;9(12):e1001356
3. World Health Organization. WHO Laboratory Manual for the Examination and Processing of Human Semen. 6th ed. WHO Press; Geneva, Switzerland: 2021 [(accessed on 3 June 2024)]. Available online: https://www.who.int/publications/i/item/9789240030787
4. Agarwal A, Baskaran S, Parekh N, Cho CL, Henkel R, Vij S, et al. *Male infertility.* Lancet. 2021;397(10271):319–333
5. Tiepolo L, Zuffardi O. Localization of factors controlling spermatogenesis in the nonflourescent portion of the human Y chromosome long arm. *Hum Genet.* 1976;34(2):119–124
6. Krausz C, Quintana-Murci L, McElreavey K. Prognostic value of Y deletion analysis: what is the clinical prognostic value of Y chromosome microdeletion analysis? *Hum Reprod.* 2000;17(7):1431–1434
7. Atlı Eİ, Mail Ç, Gürkan H, Yalçıntepe S, Demir S, Atlı E. Y chromosome polymorphism in Turkish patients with reproductive problems: a genetic centre experience. *Eur Res J*. 2023;9(4):725–729
8. Vogt PH, Edelmann A, Kirsch S, Henegariu O, Hirschmann P, Kiesewetter F, et al. Human Y chromosome azoospermia factors (AZF) mapped to different subregions in Yq11. *Hum Mol Genet [Internet]*. 1996;5(7):933–943
9. Kent-First M, Muallem A, Shultz J, Pryor J, Roberts K, Nolten W, et al. Defining regions of the Y-chromosome responsible for male infertility and identification of a fourth AZF region (AZFd) by Y-chromosome microdeletion detection. *Mol Reprod Dev*. 1999;53(1):27–41

10. Krausz C, Navarro-Costa P, Wilke M, Tüttelmann F. EAA/EMQN best practice guidelines for molecular diagnosis of Y-chromosomal microdeletions: State of the art 2023. *Andrology*. 2023;12(3):487–504
11. Skaletsky H, Kuroda-Kawaguchi T, Minx PJ, Cordum HS, Hillier L, Brown LG, et al. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature*. 2003;423(6942):825–837
12. Ferlin A, Arredi B, Speltra E, Cazzadore C, Selice R, Garolla A, et al. Molecular and Clinical Characterization of Y Chromosome Microdeletions in Infertile Men: A 10-Year Experience in Italy. *J Clin Endocrinol Metab*. 2007;92(3):762–770
13. Lange J, Skaletsky H, Bell GW, Page DC. MSY Breakpoint Map-per, a database of sequence-tagged sites useful in defining naturallyoccurring deletions in the human Y chromosome. *Nucleic Acids Res*. 2008;36:D809–D814
14. Li L, Zhang H, Yang Y, Zhang H, Wang R, Jiang Y, et al. High frequency of Y chromosome microdeletions in male infertility patients with 45,X/46,XY mosaicism. *Braz J Med Biol Res.* 2020;53(3):e8980
15. Mitra A, Dada R, Kumar R, Gupta NP, Kucheria K, Gupta SK. Y chromosome microdeletions in azoospermic patients with Klinefelter's syndrome. *Asian J Androl*. 2006;8(1):81–88
16. Shi M, Ma S, Huang L, Huang C, Wang J, Qin X, et al. Clinical Analysis of Y Chromosome Microdeletions and Chromosomal Aberrations in 1596 Male Infertility Patients of the Zhuang Ethnic Group in Guangxi. *Reprod Sci*. 2024;31(10):3074–3085
17. Akdere H, Burgazlı M. Erkek infertilitesine genetik yaklaşım. *Androloji Bülteni Erkek Üreme Sağlığı [Internet]*. 2013;15(54):207–211
18. Liu T, Song YX, Jiang YM. Early detection of Y chromosome microdeletions in infertile men is helpful to guide clinical reproductive treatments in southwest of China. *Medicine (Baltimore)*. 2019;98(5):e14350
19. Colaco S, Modi D. Genetics of the human Y chromosome and its association with male infertility. *Reprod Biol Endocrinol*. 2018;16(1):14
20. S Al-Ouqaili MT, Al-Ani SK, Alaany R, Al-Qaisi MN. Detection of partial and/or complete Y chromosome microdeletions of azoospermia factor a (AZFa) sub-region in infertile Iraqi patients with azoospermia and severe oligozoospermia. *J Clin Lab Anal*. 2022;36(3):e24272
21. Miraghazadeh A, Gilani MAS, Reihani-Sabet F, Ghaheri A, Boroujeni PB, Zamanian M. Detection of partial azfc microdeletions in azoospermic infertile men is not informative of microtese outcome. *Int J Fertil Steril*. 2019;12(4):298–302
22. Gezdirici A, Ünal I, Eröz R, Güleç EY, Ayaz İO, Çiçek G. Erkek İnfertilitesi ile Başvuran Hastalarda Spermiogram, Hormonal Profil ve Genetik Analiz Sonuçlarının Karşılaştırmalı Analizi: Tek Merkez Deneyimi. *Sağlık Bilim Değer*. 2022;12(1):15–21
23. Leslie SW, Soon-Sutton TL, Khan MAB. Male Infertility. 2024 Feb 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 32965929
24. Foresta C, Ferlin A, Gianaroli L DB. Guidelines for the appropriate use of genetic tests in infertile couples. *Eur J Hum Genet*. 2002;10(5):303–312
25. Ağırbaşlı D, Erdoğan Erdur G, Seven M, Kalaycı Yiğin A. Frequency of Y Chromosome Microdeletions in Turkish Infertile Men: Single Center Experience (Türk İnfertil Erkeklerde Y kromozomu Mikrodelesyonlarının Sıklığı: Tek Merkez Deneyimi). *Genel Tıp Derg*. 2022;32(6):737–739
26. Andersen PS, Jespersgaard C, Vuust J, Christiansen M, Larsen LA. Capillary electrophoresis-based single strand DNA conformation analysis in high-throughput mutation screening. *Hum Mutat*. 2003;21(5):455–465
27. Bustin SA, Benes V, Garson JA, Hellemans J, Huggett J, Kubista M, et al. The MIQE guidelines: minimum information for publication of quantitative real-time PCR experiments. *Clin Chem*. 2009;55(4):611–622
28. Cao H, Shockey JM. Comparison of TaqMan and SYBR green qPCR methods for quantitative gene expression in tung tree tissues. *J Agric Food Chem*. 2012;60(50):12296–12303
29. Kralik P, Ricchi M. A Basic Guide to Real Time PCR in Microbial Diagnostics: Definitions, Parameters, and Everything. *Front Microbiol*. 2017 Feb 2;8:108
30. Simoni M, Tüttelmann F, Gromoll J, Nieschlag E. Clinical consequences of microdeletions of the Y chromosome: the extended Münster experience. *Reprod Biomed Online*. 2008;16(2):289–303
31. Ghanami Gashti N, Sadighi Gilani MA, Abbasi M. Sertoli cell-only syndrome: etiology and clinical management. *J Assist Reprod Genet*. 2021;38(3):559–572
32. Krausz C, Degl'Innocenti S, Nuti F, Morelli A, Felici F, Sansone M, et al. Natural transmission of USP9Y gene mutations: A new perspective on the role of AZFa genes in male fertility. *Hum Mol Genet*. 2006;15(18):2673–2681
33. Luddi A, Margollicci M, Gambera L, Serafini F, Cioni M, De Leo V, et al. Spermatogenesis in a manwith complete deletion of USP9Y. *N Engl J Med*. 2009;360(9):881–885
34. Yuen W, Golin AP, Flannigan R SP. Histology and sperm retrieval among men with y chromosome microdeletions. *Transl Androl Urol*. 2021;10(3):1442–1456
35. Romo-Yáñez J, Sevilla-Montoya R, Pérez-González E, Flores-Reyes J, Laresgoiti-Servitje E, Espino-Sosa S, et al. AZFa, AZFb, AZFc and gr/gr Y-chromosome microdeletions in azoospermic and severe oligozoospermic patients, analyzed from a neural network perspective. *Cir Cir*. 2022;90(2):202–209
36. Kleiman SE, Yogev L, Lehavi O, Hauser R, Botchan A, Paz G, et al. The likelihood of finding mature sperm cells in men with AZFb or AZFb-c deletions: six new cases and a review of the literature (1994–2010). *Fertil Steril*. 2011;95(6):2005–2012
37. Lin YM, Lin YH, Teng YN, Hsu CC, Shinn-Nan Lin J, Kuo PL. Gene-based screening for Y chromosome deletions in Taiwanese men presenting

with spermatogenic failure. *Fertil Steril*. 2002;77(5):897–903
38. Costa P, Gonçalves R, Ferrás C, Fernandes S, Fernandes AT, Sousa M, Barros A. Identification of new breakpoints in AZFb and AZFc. *Mol Hum Reprod*. 2008;14(4):251–258
39. Stouffs K, Vloeberghs V, Gheldof A, Tournaye H, Seneca S. Are AZFbdeletions always incompatible with sperm production? *Andrology*. 2017;5(4):691–694
40. Vogt PH, Bender U, Deibel B, Kiesewetter F, Zimmer J, Strowitzki T. Human AZFb deletions cause distinct testicular pathologies depending on their extensions in Yq11 and the Y haplogroup: new cases and review of literature. *Cell Biosci*. 2021;11(1):60
41. Vogt PH, Fernandes S. Polymorphic DAZ gene family in polymorphic structure of AZFc locus: Artwork or functional for human spermatogenesis? *APMIS*. 2003;111(1):115–126
42. Yen PH. Putative biological functions of the DAZ family. *Int J Androl*. 2004;27(3):125–129
43. Fernandes S, Paracchini S, Meyer LH, Floridia G, Tyler-Smith C, Vogt PH. A large AZFc deletion removes DAZ3/DAZ4 and nearby genes from men in Y haplogroup N. *Am J Hum Genet*. 2004;74(1):180–187
44. Repping S, Skaletsky H, Brown L, van Daalen SK, Korver CM, Pyntikova T, et al. Polymorphism for a 1.6-Mb deletion of the human Y chromosome persists through balance between recurrent mutation and haploid selection. *Nat Genet*. 2003;35(3):247–251
45. Patsalis PC, Sismani C, Quintana-Murci L, Taleb-Bekkouche F, Krausz C, McElreavey K. Effects of transmission of Y chromosome AZFc deletions. *Lancet*. 2002;360(9341):1222–1224
46. Lange J, Skaletsky H, van Daalen SK, Embry SL, Korver CM, Brown LG, et al. Isodicentric Y chromosomes and sex disorders as byproducts of homologous recombination that maintains palindromes. *Cell*. 2009;138(5):855–869
47. Krausz C, Giachini C, Xue Y, O'Bryan MK, Gromoll J, Rajpert-de Meyts E, et al. Phenotypic variation within European carriers of the Y-chromosomal gr / gr deletion is independent of Y-chromosomal background. *J Med Genet*. 2009;46(1):21–31
48. Dutta S, Paladhi P, Pal S, Srimani S, Bose G, Ghosh P, et al. Screening of the Combined Risk of Genetics and Epidemiology on Infertility Among Indian Men: Synergistic Effect of AZFc Partial Deletions and Habits of Smokeless Chewing Tobacco. *Am J Mens Health*. 2024;18(5):15579883241279196
49. Zenteno-Ruiz JC, Kofman-Alfaro S, Méndez JP. 46, XX sex reversal. *Arch Med Res*. 2001;32(6):559–566
50. Ergun-Longmire B, Vinci G, Alonso L, Matthew S, Tansil S, Lin-Su K, et al. Clinical, Hormonal and Cytogenetic Evaluation of 46,XX Males and Review of the Literature. *J Pediatr Endocrinol Metab*. 2005;18(8):739–748

Osmangazi Journal of Med, 2025;47(1): 128-132
DOI: 10.20515/otd.1592522

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Ten-Year Experience with Atraumatic Splenic Rupture in a Tertiary University Hospital

Üçüncü Basamak Bir Üniversite Hastanesinde Atravmatik Dalak Rüptürü ile İlgili On Yıllık Deneyim

Akile Zengin[1], Mithat Mert Yurdakul[2], Yavuz Selim Angın[2], Murat Ulaş[1]

[1]Department of Gastrointestinal Surgery, Eskisehir Osmangazi University, Eskisehir, Türkiye
[2]Department of General Surgery, Eskisehir Osmangazi University, Eskisehir, Türkiye

ORCID ID of the authors
AZ. 0000-0003-0981-8901
MMY 0009-0002-8816-8256
YSA. 0000-0001-5315-8360
MU. 0000-0002-3507-8647

Correspondence / Sorumlu yazar:
Akile ZENGİN

Department of Gastrointestinal Surgery, Eskisehir Osmangazi University, Eskisehir, Türkiye

e-mail: dr.akile.zengin@gmail.com

Abstract: In this present study, we aim to share our clinical experience in patients with atraumatic splenic rupture (ASR). The records of all patients were reviewed from January 2015 to May 2024, retrospectively. We had 8 patients diagnosed with ASR. Of the patients 62.5% (n=5) were female. The median age was 52.5 (37-72) years. Three patients had a history of malignancy, two had hematologic disease, and three had autoimmune disease.Two patients had previously undergone abdominal surgery.Two patients had a history of oral anticoagulant use.The median onset of symptoms was 16 (1-168) hours. Splenomegaly was detected in three patients via computed tomography. In one patient, a distal pancreatectomy was performed in addition to splenectomy, while for another patient, distal pancreatectomy, gastric wedge resection, and packing were performed. The median operation time was 122.5 (60-210) min. The median hospital stay was 8.5 (1-41) days. Pathological results showed adenocarcinoma metastasis in one patient (due to endometrial cancer), and necrotising granulomatous inflammation in one patient (due to abdominal tuberculosis). Early postoperative complication was seen only one patient as pancreatic fistula. Mortality occurred in three patients. One patient died in the second postoperative hour from hypovolemic shock, another from sepsis, and the third from a subarachnoid hemorrhage. Despite its clinically vague presentation,the diagnosis of spontaneous splenic rupture should be considered in patients with no history of trauma but who present with hypovolemic shock,acute abdomen or abdominal pain of unknown etiology.
Keywords: Acute Abdomen, Spontaneus Spleen Ruptur, Nontraumatic Splenic Damage, İntraabdominal Hemorrhage

Özet: Bu çalışmada, atravmatik dalak rüptürü (ASR) olan hastalardaki klinik deneyimimizi paylaşmayı amaçlıyoruz. Tüm hastaların kayıtları Ocak 2015'ten Mayıs 2024'e kadar retrospektif olarak incelendi. ASR tanısı konulan 8 hastamız vardı.. Hastaların %62.5'i (n=5) kadındı. Ortanca yaş 52.5 (37-72) yıldı. Üç hastada malignite öyküsü, iki hastada hematolojik hastalık ve üç hastada otoimmün hastalık vardı. İki hasta daha önce karın ameliyatı geçirmişti. İki hastada oral antikoagülan kullanma öyküsü vardı. Semptomların başlangıcı ortanca 16 (1-168) saatti. Üç hastaya Epstein-Barr Virüsü ve Sitomegalovirüs testleri yapıldı ve tümünde sonuç negatifti. Üç hastada bilgisayarlı tomografi ile splenomegali tespit edildi. Bir hastada splenektomiye ek olarak distal pankreatektomi yapılırken, bir diğer hastaya distal pankreatektomi, gastrik wedge rezeksiyon ve packing yapıldı. Operasyon süresi ortanca 122.5 (60-210) dakikaydı. Ortanca hastanede kalış süresi 8.5 (1-41) gündü. Patolojik sonuçlar bir hastada adenokarsinom metastazı (endometriyal kanser nedeniyle) ve bir hastada nekrotizan granülomatöz inflamasyondu (abdominal tüberküloz nedeniyle). Ameliyat sonrası erken komplikasyon sadece bir hastada pankreas fistülü olarak görüldü. Üç hastada mortalite görüldü. Bir hasta postoperatif ikinci saatte hipovolemik şoktan, bir diğeri sepsis nedeniyle ve üçüncüsü subaraknoid kanama nedeniyle öldü. Klinik olarak belirsiz sunumuna rağmen, travma öyküsü olmayan ancak hipovolemik şok, akut karın veya etiyolojisi bilinmeyen karın ağrısı ile gelen hastalarda spontan dalak rüptürü tanısı düşünülmelidir.
Anahtar Kelimeler: Akut Karın, Spontan Dalak Rüptürü, Travmatik Olmayan Dalak Hasarı, İntraabdominal Kanama

Ethics Committee Approval: This study was approved by the Ethics Committee of the Eskisehir Osmangazi University (Decision no: 15, Date: 03.10.2024).

Informed Consent: The authors declared that informed consent form was signed by the patient.

Authorship Contributions: All authors contributed equally to the study.

Copyright Transfer Form: Copyright Transfer Formwas signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Received : 27.11.2024

Accepted :06.01.2025

Published : 07.01.2025

How to cite/ Atıf için: Zengin A, Yurdakul MM, Angın YS, Ulaş M, Ten-Year Experience with Atraumatic Splenic Rupture in a Tertiary University Hospital, Osmangazi Journal of Medicine, 2025;47(1):128-132

1. Introduction

Atraumatic splenic rupture (ASR) is rare but life-threatening, with a high risk of mortality, making it a critical emergency (1). In cases of acute abdominal pain without a history of trauma, ASR is often overlooked in the differential diagnosis (2).

In the literature, rupture without a history of trauma is commonly referred to as "spontaneous" or "atraumatic" rupture (3). However, this terminology can be misleading. In 1991, Crate and Payne (4) defined spontaneous splenic rupture as occurring in the absence of trauma or exertion, without any underlying disease affecting the spleen, and with no evidence of prior splenic trauma or rupture (such as adhesions or scarring). Furthermore, their criteria required that the spleen appear normal upon macroscopic and histological examination and that there be no findings suggesting acute or convalescent phase antibody titers linked to viral infections affecting the spleen. Thus, while all spontaneous splenic ruptures fall within the ASR category, not all ASR cases qualify as spontaneous ruptures. Therefore, in this paper, we will refer to cases that other authors may have labeled as "spontaneous splenic rupture" under the umbrella term ASR.

This study aims to identify the characteristics, etiology, and diagnostic and therapeutic processes in our patients with ASR, as well as to highlight our approach to these less commonly encountered cases.

2. Materials and Methods

This study was approved by the local ethics committee (2024/15). Inclusion criteria were age >18 years and emergency splenectomy due to splenic rupture without a history of trauma. Patients who underwent elective open/laparoscopic splenectomy and splenectomy due to iatrogenic splenic injury during other surgeries were excluded from the study. Ultimately, eight patients met the criteria and were included in the study. A length of 12 to 20 cm is indicative of splenomegaly (measurements by ultrasonography (USG) or computed tomography (CT) (5).

Age, gender, The American Society of Anesthesiologists classification (ASA), comorbities, previous surgery history, oral anticoagulant use history, onset of sign, hemoglobin (Hb), hematocrit (Htc), white blood cell (WBC), lymphocyte, platelet (Plt), international normalized ratio (INR), amylase, viral marker (Epstein-Barr Virus (EBV), Cytomegalovirus (CMV) levels, imaging methods, presence of splenomegaly as radiologically, operation type, combined resection, hospital mortality, and pathological results were analyzed.

Statistic

Continuous variables are reported as medians (range), and categorical data are presented as frequencies and percentages.

3. Results

A total of 285 patients underwent splenectomy, with or without additional organ resection, between January 2015 and May 2024, and 8 patients were diagnosed with ASR.

Table 1 shows the demographic data and preoperative biochemical test results of the patients. Of the patients, 62.5% (n=5) were female. The median age was 52.5 (37-72) years. One patient had secondary metastatic neoplasia (endometrial cancer), one had a malignant hematologic disease (acute myeloid leukemia [AML]), and one had a primary neoplastic disease (mesothelioma). Two patients had non-malignant hematologic conditions (disseminated intravascular coagulation [DIC] and idiopathic thrombocytopenic purpura [ITP]), while three had a history of autoimmune disease (systemic lupus erythematosus [SLE], ankylosing spondylitis, and Crohn’s disease). No underlying cause was identified in two patients.

Two patients had history of prior abdominal surgery (appendectomy and laparoscopic cholecystectomy), and two patients had history of oral anticoagulant use. The median onset of symptoms was 16 (1-168) hours. Patient 5 presented to the hospital with a three-week history of dyspnea. A CT scan revealed a splenic laceration incidentally. Patient 6’s delayed diagnosis was due to the patient’s hospitalization in the hematology ward at the time of consultation and the very late onset of symptom. EBV and CMV tests were conducted on three patients, and results were negative in all cases.

Diagnosis methods and follow-up outcomes of the patients are shown in Table 2. Splenomegaly was detected for three patients in CT. In Patient 5, a distal pancreatectomy was performed in addition to a splenectomy, while for Patient 7, distal pancreatectomy, gastric wedge resection, and packing were performed. The others were performed only splenectomy. The median operation time was

122.5 (60-210) minutes. The median hospital stay was 8.5 (1-41) days. Pathological results showed adenocarcinoma metastasis in one patient (due to endometrial cancer), and necrotising granulomatous inflammation in one patient (due to abdominal tuberculosis), the others pathological results were reported normal spleen tissue.

Patient 8 underwent two reoperations. The first was for atraumatic splenic rupture, during which splenectomy, distal pancreatectomy, gastric wedge resection, and packing were performed. On the second postoperative day, the patient was reoperated for depacking. An early postoperative complication included a pancreatic fistula, for which interventional radiology placed an external stent to manage the leakage. However, on the 22nd postoperative day, abdominal bleeding occurred, necessitating a third surgery. No focus detected.

Mortality occurred in three patients on postoperative 0th (Patient 4), 8th (Patient 3), and 20th (Patient 6) day. Patient 4 died in the second postoperative hour from hypovolemic shock, Patient 3 died of sepsis, and Patient 2 died from a subarachnoid hemorrhage.

Table 1. Demographic data and preoperative biochemical test results of the patients

Patient number	**P-1**	**P-2**	**P-3**	**P-4**	**P-5**	**P-6**	**P-7**	**P-8**
Age (year)	54	50	38	60	68	72	51	37
Gender (F/M)	F	M	F	F	F	F	M	M
ASA	2	2	2	2	3	2	2	2
Comorbidities	Endometrial cancer, DIC, Asthma	Ankylosing spondylitis	Mesothelioma	SLE, ITP	HT, CAD	AML	CRD	Chron diseas e
Previous surgery	Appendectomy	-	Left pneumonuctomy	Thyroidectomy	Laparoscopic cholecystectomy, menengioma resection	-	-	-
Oral anticoagulant use history (+/-)	+	-	-	-	+	-	-	-
Onset of sign (hour)	6	72	16	1	incidental	168	8	28
Hb (g/dl)	8.5	6.5	5.9	4.5	8.5	5	6.7	8.8
Htc (%)	26.6	28.8	17.7	13	24.6	14.7	19.4	25.7
WBC (10^3/uL)	27800	13620	22200	39900	23030	530	26070	24720
Lymphocyte (/mm^3)	2300	2530	400	3900	1130	280	2120	1060
Plt ((/mm^3)	391000	204000	90000	21000	389000	20000	71000	297000
INR	1,34	1,22	1,30	1,26	1,31	1,17	1,4	1,07
Amylase (U/L)	34	59	12	56	43	25	142	49
Viral markers (CMV/EBV)	NA	negative	NA	NA	NA	NA	negative	negative

F: Female, M: Male, The American Society of Anesthesiologists classification, DIC: Disseminated intravascular coagulation, HT: Hypertension, SLE: Systemic lupus erythematosus, ITP: Idiopathic thrombocytopenic purpura, CAD: Coronary artery disease, AML: acute myeloid leukemia, CRD: chronic renal disease, Hb: Hemoglobin, Htc: Hematocrit, WBC: White blood cell, Plt: Platelet, INR: International normalized ratio EBV: Epstein-Barr Virus, CMV: Cytomegalovirus, NA:nonavailable

Table 2. Diagnosis methods and follow-up outcomes of the patients.

Patient number	**P-1**	**P-2**	**P-3**	**P-4**	**P-5**	**P-6**	**P-7**	**P-8**
Imaging methods	CT	USG, CT	USG, CT	CT	CT	USG, CT	USG, CT	CT
Splenomegaly (+/-)	-	-	-	-	+	+	+	-
Operation type	Splenectomy	Splenectomy	Splenectomy	Splenectomy	Splenectomy + Distal pancreatectomy	Splenectomy	Splenectomy+ Distal pancreatectomy + gastric wedge resection+ Packing	Splenectomy
Hospital mortality	-	-	Po 8th day	Po 0th day	-	Po 20th day	-	-
Pathological results	Adenocarcinoma (metastatic)	N	N	N	N	N	N	Necrotising granulomatous inflammation

P: Patient, CT: Computed tomography, USG: Ultrasonography, Po: postoperative, N: normal, NA: nonavailable

4. Discussion

The most common cause of ASR in the literature is neoplastic disease (1). The results of our study indicate that, consistent with previous findings, splenic rupture associated with neoplastic disorders is quite common reason for ASR.

The major causes of ASR are classified as neoplastic disorders (including hematologic, benign, or malignant spleen-related diseases), infectious diseases, inflammatory noninfectious diseases, drug- and treatment-related conditions, mechanical issues, and, lastly, cases involving a normal spleen (1). ASR can occur due to pathological stimuli affecting the spleen or in situations such as sneezing, coughing, vomiting, straining during defecation, or physical exertion (3,6).

In hematological diseases, splenomegaly due to extramedullary hematopoiesis can increase the risk of secondary ASR (7)**.** ASR was diagnosed a patient in the 3rd trimester (mechanical disorder) with thrombocytopenic purpura (non-malignant hematological disease) in the literature. We can give this case report as an example of the etiologies that can be seen together. (8). Similarly, two of our patients had a multifactorial etiology (malignancy and hematological disease, and hematological disease and aoutoimmune disease). We also had two patients (25%) with ASR in a normal spleen, which could be considered spontaneous rupture. Although our sample size is small, the rate of spontaneous splenic rupture in our clinic was higher than reported in the literature (25% vs. 6.4%) (3).

It is well-established that ASR is associated with infectious diseases, particularly viral infections. The literature includes reports of ASR cases linked to EBV (for which physical activity is restricted for at least one month to prevent ASR) (9), CMV (10), tuberculosis (11), malaria (12)**,** systemic salmonella infection (13), scrub typhus (14). In one patient abdominal tuberculosis was detected pathologically, and unfortunately, only three patients were evaluated with viral panels, and no active infections were detected in these cases. Through this study, we determined that ASR etiology screening in our clinic was deficient in sending viral panels, and addressed this through enhanced in-service training.

In the literature, ASR has also been reported following intra-abdominal surgery. Examples include cases of ASR secondary to bacteremia one week after an appendectomy (15), and two weeks after a laparoscopic sleeve gastrectomy (16). In our study, no ASR cases were identified in association with prior abdominal surgery.

Since ASR clinical findings can be nonspecific, imaging modalities are essential for distinguishing it from other etiologies (17). For hemodynamically unstable patients, Focused Assessment With Sonography in Trauma (FAST) USG is preferred as a rapid and non-invasive diagnostic imaging method. (7) USG is an useful first-line imaging method for detecting free intraperitoneal blood; however, its sensitivity is low while diagnosing splenic rupture (3)**.** Multidetector CT could be primary imaging method for detecting lesions in the spleen, active bleeding, and perisplenic hemorrhage (3). Magnetic

resonance imaging, while more sensitive in detecting small intraparenchymal hemorrhages, has limited use in emergency situations due to its longer imaging time and the need for the patient to remain stable during the procedure (17).

The management of ASR, whether conservative or surgical, is related to the integrity of the splenic capsule. Patients with low-grade injuries who are hemodynamically stable can be managed conservatively (with splenic artery embolization), while surgical intervention is required for hemodynamically unstable patients (18).

5. Conclusion

In conclusion, despite its clinically vague presentation, the diagnosis of spontaneous splenic rupture should be considered in patients with no history of trauma but who present with hypovolemic shock, acute abdomen, or abdominal pain of unknown etiology, along with a history of hematological malignancy, autoimmune diseases, or infectious diseases. Delayed diagnosis may lead to mortality.

REFERENCES

1. Renzulli P, Hostettler A, Schoepfer AM, Gloor B, Candinas D. Systematic review of atraumatic splenic rupture. J Br Surg. 2009;96:1114–21.
2. Kocael PC, Simsek O, Bilgin IA, Tutar O, Saribeyoglu K, Pekmezci S, et al. Characteristics of patients with spontaneous splenic rupture. Int Surg. 2014;99:714–8.
3. Gómez-Ramos JJ, Marín-Medina A, Lisjuan-Bracamontes J, García-Ramírez D, Gust-Parra H, Ascencio-Rodríguez MG. Adolescent with spontaneous splenic rupture as a cause of hemoperitoneum in the Emergency Department: case report and literature review. Pediatr Emerg Care. 2020;36:e737–41.
4. Crate ID, Payne MJ. Is the diagnosis of spontaneous rupture of a normal spleen valid? J R Army Med Corps. 1991;137:50–1.
5. Chapman J, Goyal A, Azevedo AM. Splenomegaly. (StatPearls Publishing, 2022)
6. Reinhold GW, Melonakos TK, Lyman DT. A near fatal sneeze spontaneous splenic rupture: a case report and review of the literature. Clin Pract Cases Emerg Med. 2017;1:190-3.
7. Odabaş EN, Topçuoğlu H, Aydoğan T, Özer V, Karaca Y. A rare cause of abdominal pain: Spontaneous rupture of the spleen. J Surg Med. 2021;5:389–91.
8. Xu H, Lu JP. Spontaneous rupture of the spleen at full term during pregnancy: a case report. J Int Med Res. 2023;51:1-5.
9. Fugl A, Andersen CL. Epstein-Barr virus and its association with disease - a review of relevance to general practice. BMC Fam Pract. 2019;20:1-8.
10. Maria V, Saad AM, Fardellas I. Spontaneous Spleen Rupture in a Teenager: An Uncommon Cause of Acute Abdomen. Case Rep Med. 2013;2013:1–3.
11. Marcos-Ramírez ER, Treviño-García LA, Téllez-Aguilera A, Molina-Ayala M, Flores-Gutiérrez JP, Salinas-Domínguez R, et al. Spontaneous splenic rupture, an unusual presentation of tuberculosis. Cir Cir. 2021;89:1–5.
12. Weinberg Y, Feldman A, Jakobson DJ, Mishal J. Spontaneous Pathologic Splenic Rupture in a Patient with Plasmodium falciparum Infection, First Case Reported in Israel. Infect Dis Rep. 2020;12:121–6.
13. Wolthuis DF, Bosboom RW, Hassing RJ. Spontaneous splenic rupture in an ill returned traveller. Eur J Case Rep Intern Med. 2020;7:1-3.
14. Hwang HP, Kim KM, Han H, Hwang JH. Spontaneous splenic rupture associated with scrub typhus: a case report. Infect Dis Poverty. 2024 Jan 22;13:1-7.
15. Deleuze C, Rasmont C, Ivanov T, Brassart N, Ghaddab M, Romero Stoca L, et al. A case of splenic rupture a week after appendectomy. J Surg Case Rep. 2021;12:1-3.
16. Sandal M, Hussein BA, Buti F, Al Marzouqi O, Khammas A. Spontaneous splenic rupture two weeks after sleeve gastrectomy. Obes Surg. 2020;30:3226–8.
17. Jain D, Lee B, Rajala M. Atraumatic splenic hemorrhage as a rare complication of pancreatitis: case report and literature review. Clin Endosc. 2020;53:311–20.
18. Gregory R. A Near Fatal Sneeze Spontaneous Splenic Rupture: A Case Report and Review of the Literature. 2017;1:190-3.

Osmangazi Journal of Med, 2025;47(2):133-139
DOI: 10.20515/otd.1570023

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Testis Kanserinde Hematolojik Parametrelerin Tani Yöntemleri İle Olan İlişkisi

Relationship Between Diagnostic Methods And Hematological Parameters In Testicular Cancer

[1]Veli Mert Yazar, 2Arif Bedirhan Bayraktar, [1]Osman Gerçek, [1]Melih Şenkol

[1]Afyonkarahisar Sağlık Bilimleri Üniversitesi, Tıp Fakültesi, Üroloji Anabilim Dalı,Afyonkarahisar, Türkiye
[2]Yozgat Şehir Hastanesi, Üroloji Kliniği, Yozgat, Türkiye

ORCID ID of the authors
VM. 0000-0001-7885-1401
ABB. 0000-0002-2373-5929
OG. 0000-0002-8710-7171
MŞ. 0009-0007-4714-8028

Correspondence / Sorumlu yazar:
Veli Mert YAZAR

Afyonkarahisar Sağlık Bilimleri Üniversitesi, Tıp Fakültesi, Üroloji Anabilim Dalı,Afyonkarahisar, Türkiye

e-mail: vmyazar@gmail.com

Etik Kurul Onayı: Çalışma Afyonkarahisar Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulu tarafından onaylanmıştır. Karar no: 2024/4-144 Tarih: 07.06.2024
Telif Hakkı Devir Formu: Tüm yazarlar tarafından Telif Hakkı Devir Formu imzalanmıştır.
Yazar Katkısı: Cerrahi ve Tıbbi Uygulamalar: VMY, OG. Konsept: VMY, ABB. Tasarım: OG, MŞ. Veri Toplama veya İşleme: VMY, MŞ. Analiz veya Yorum: OG, ABB. Literatür Taraması: VMY,OG,MŞ. Yazma: VMY,OG,ABB.
Çıkar Çatışması Beyanı: Yazarlar arasında herhangi bir çıkar çatışması bulunmamaktadır.
Destek ve Teşekkür Beyanı: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received : 18.10.2024
Accepted : 13.01.2025
Published : 14.01.2025

Abstract: Testicular cancer is the most common solid malignancy in young adult males. The aim of this study is to investigate the relationship between hematological parameters in testicular tumors and traditional methods used in diagnosis. Sixty-eight patients who underwent radical orchiectomy due to testicular tumor were retrospectively analyzed. Age, presenting complaint, tumor side, radiological tumor size, pathological tumor size, preoperative tumor markers (AFP, β-hCG, LDH) of the patients were recorded. In addition preoperative hemogram parameters of the patients; WBC, neutrophil, lymphocyte, monocyte, basophil, eosinophil, hemoglobin, platelet, mean corpuscular volume , mean platelet volume, platelet distribution width were recorded. In addition, systemic inflammatory markers obtained from hemogram parameters such as neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, monocyte-lymphocyte ratio, monocyte-platelet ratio, systemic immune-inflammatory index, systemic inflammatory response index, systemic inflammatory aggregate index were calculated and recorded. When hematological parameters were examined; lymphocyte count was determined as 2.26±0.58 ×103/μL in the seminoma group and was significantly higher than in the non-seminoma group (p=0.020). WBC, MCV, MPV, PDW, neutrophil, monocyte basophil, eosinophil and hemoglobin and platelet values were similar in both groups (all p>0.05). NLR, PLR, SII values were observed to be higher in the non-seminoma group and MPR value was observed to be higher in the seminoma group (p=0.03, p=0.004, p=0.01, p=0.04, respectively). Inflammation indices derived from complete blood count are low-cost, reliable and easily accessible parameters that do not require additional examination. These indices can be used to predict histological subgroups of germ cell testicular tumors before surgery and to support pathological diagnosis.
Keywords: Testicular Tumor, Neutrophil, Germ Cell Tumors

Özet: Testis kanseri, genç yetişkin erkeklerde en sık görülen solid malignitedir. Bu çalışmanın amacı testis tümörlerindeki meydana gelen hematolojik parametrelerin, tanıda kullanılan geleneksel yöntemler ile ilişkisini araştırmaktadır. Testis tümörü nedeniyle radikal orşiektomi uygulanan 68 hasta retrospektif olarak incelendi. Hastaların yaş, başvuru şikayeti, tümör tarafı, radyolojik tümör boyutu, patolojik tümör boyutu, preoperatif tümör belirteçleri (AFP, β-hCG. LDH) kaydedildi. Ayrıca hastaların preoperatif hemogram parametrelerinden; WBC, nötrofil, lenfosit, monosit, bazofil, eozinofil, hemoglobin, platelet, ortalama korpüsküler hacim, ortalama trombosit hacmi, platelet dağılım genişliği değerleri kaydedildi. Ayrıca hemogram parametrelerinden elde edilen sistemik inflamatuvar belirteçler olan nötrofil lenfosit oranı, platelet lenfosit oranı, monosit lenfosit oranı, monosit platelet oranı, sistemik immün-inflamatuar indeks, sistemik inflamatuar response indeks, sistemik inflamatuar agregat indeks değerleri hesaplandı ve kaydedildi. Hematolojik parametreler incelendiğinde; lenfosit sayısı seminom grubunda 2,26±0,58 ×103/μL olarak saptanmış olup, non-seminom grubuna göre anlamlı yüksekti (p=0,020). WBC, MCV, MPV, PDW, nötrofil, monosit bazofil, eozinofil ve hemoglobin ve platelet değerleri her iki grupta benzerdi (hepsi p>0,05). NLR, PLR, SII değerleri non-seminom grubunda, MPR değeri ise seminom grubunda yüksek izlenmiştir (sırasıyla; p=0,03, p=0,004, p=0,01, p=0,04). Tam kan sayımından türetilen inflamasyon indeksleri ek tetkik gerektirmeyen maliyet düşük, güvenilir ve kolayca erişilebilir parametrelerdir. Bu indeksler ameliyat önce germ hücreli testis tümörlerinin histolojik alt gruplarını öngörme ve patolojik tanıyı destekleme amacıyla kullanılabilir.
Anahtar Kelimeler: Testis tümörü, Nötrofil, Germ hücreli tümörler

How to cite/ Atıf için: Yazar VM, Bayraktar AB, Gerçek O, Şenkol M, Testis Kanserinde Hematolojik Parametrelerin Tani Yöntemleri İle Olan İlişkisi, Osmangazi Journal of Medicine, 2025;47(2):133-139

1. Giriş

Testis kanseri, genç yetişkin erkeklerde en sık görülen solid malignitedir. Erişkin kanserlerinin %1'ini ve ürolojik kanserlerin %5'ini oluşturmaktadır (1, 2). Olguların %90-95'ini germ hücreli tümörler (GHT) oluşturmaktadır ve tanı anında %1-2'si bilateraldir. En sık görüldüğü yaş, non-seminom (NS) ve miks GHT'ler için üçüncü dekat ve seminom için dördüncü dekattır (2). Cerrahi tedavi ile etkili bir şekilde tedavi edilebilmesi ve %95'in üzerinde 5 yıllık sağkalım oranlarına sahip olması nedeniyle erken teşhis ve tedavi önemlidir (3). Testis kanserinin kesin nedenleri tam olarak anlaşılamamıştır ancak yaş, kriptorşidizm, anormal testis gelişimi, kişisel ve ailede testis kanseri öyküsü, etnik köken ve immün sistem bozuklukları gibi çeşitli risk faktörleri tanımlanmıştır (4). Tanıda fizik muayene, radyolojik görüntüleme ve tümör belirteçleri kullanılmaktadır. Testis kanseri genellikle ağrısız testis kitlesiyle veya ultrasonda (USG) rastlantısal olarak ortaya çıkar (5). Alfa-fetoprotein (AFP), β-hCG ve laktat dehidrogenaz (LDH), testis kanseri tanısını desteklemede, kanser evrelemesinde ve risk sınıflandırmasında kullanıldıkları için orşiyektomi öncesi ve sonrası bakılmalıdır (6). Ancak bu belirteçler çok spesifik değildir; AFP ve β-hCG, sırasıyla non-seminomatöz germ hücreli tümörlü hastaların %50-70'inde ve %40-60'ında artarken, β-hCG yüksekliği seminomların sadece %30'unda tespit edilebilmektedir (7). Daha iyi evreleme yapılması, serum tümör belirteçlerinin kullanılması ve birçok prognostik faktörlerin tanımlanmasına rağmen testis kanseri halen bazı hastalarda ölümcül olabilmektedir. Bu nedenle diğer kanser türlerinde olduğu gibi testis kanserinde de farklı prognostik faktörlerin araştırılmıştır. İnflamasyon; tümör gelişiminde, rekürrens ve prognozunda kritik rol oynamaktadır (8). İnflamatuar sürecin etkisi görülen kanserler türlerinde nötrofil-lenfosit,trombosit-lenfosit veya lenfosit-monosit oranları da dahil edilmek olmak üzere hematolojik parametrelerin kanserlerin özellikle tanı ve prognozda kullanılabildiği gösterilmiştir (9, 10). Biz bu çalışmamızda, testis kanserinin tanısında kullanılan geleneksel yöntemler ile hematolojik parametreler ile ilişkisini araştırdık.

2. Gereç ve Yöntem

Çalışma Dizaynı

Çalışmamıza etik kurul onay alındıktan sonra (xxx Üniversitesi Klinik Araştırmalar Etik Kurulu. 2011-KAEK-2, 2024/144) Nisan 2013 – Nisan 2023 tarihleri arasında Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Üroloji Kliniği'nde testis tümörü nedeniyle radikal inguinal orşiektomi uygulanan 18- 60 yaş arası 68 hasta retrospektif olarak incelendi. Çalışmamız Helsinki Deklarasyonu ilkelerine uygun olarak yapıldı. Non-germ hücreli testis tümörü, bilateral testis tümörü, akut enfeksiyon, kronik inflamatuar hastalık, malignite veya hematolojik bozukluğu olan hastalar, antikoagülan tedavi alanlar ve son bir ay içerisinde kan ürünü uygulanan hastalar çalışma dışı bırakıldı. Hastaların; yaş, başvuru şikayeti, tümör tarafı, radyolojik tümör boyutu, patolojik tümör boyutu, preoperatif tümör belirteçleri (AFP, β-hCG. LDH) ve hemogram parametreleri kaydedildi. Histolojik alt tipler, Dünya Sağlık Örgütü'nün tanımladığı sınıflamaya göre, evreleme ise Uluslararası Kanserle Mücadele Birliği'nin (UICC) 2016 Tümör, Nod, Metastaz (TNM) sınıflandırmasına göre yapıldı (11). Hastaların preoperatif hemogram parametrelerinden; beyaz kan hücreleri (WBC), nötrofil, lenfosit, monosit, bazofil, eozinofil, hemoglobin, platelet, ortalama korpüsküler hacim (MCV), ortalama trombosit hacmi (MPV), platelet dağılım genişliği (PDW) değerleri kaydedildi. Ayrıca hemogram parametrelerinden elde edilen sistemik inflamatuvar belirteçler olan nötrofil lenfosit oranı (NLR), platelet lenfosit oranı (PLR), monosit lenfosit oranı (MLR), monosit platelet oranı (MPR), sistemik immün-inflamatuar indeks (SII) (nötrofilxplatelet/lenfosit), sistemik inflamatuar response indeks (SIRI) (nötrofilxmonosit/lenfosit), sistemik inflamatuar agregat indeks (AISI) (nötrofilxmonosit/lenfosit) değerleri hesaplandı ve kaydedildi. Patoloji sonucuna göre seminom saptananlar ile non-seminom testis tümörü saptanan hastalar iki gruba ayrıldı. Bu iki grupta, hematolojik sistemik inflamatuar belirteçlerin, testis tümörü tanısında ve histolojik tip öngörüsünde tanısal değerinin incelenmesi amaçlandı.

İstatistiksel Analiz

Çalışma verilerinin istatistiksel analizi bilgisayar ortamında IBM SPSS (Statistical Package for the Social Sciences) version 20.0 programı ile yapıldı. Değişkenlerin normal dağılıma uygunluğu Kolmogorov-Smirnov (K-S) testi kullanılarak incelendi. İkili grupların karşılaştırılmasında; normal dağılım gösteren parametreler için Student's t testi, anormal dağılım gösteren parametreler için Mann-Whitney U testi uygulandı. Çok gözlü çapraz

tabloların değerlendirilmesi Ki-kare testi ya da Fisher Exact testi ile yapıldı. Tümör boyutu, evresi, tümör belirteçleri ve hematolojik parametreler arası ilişkiler yerine göre Spearman korelasyon testi ve Pearson korelasyon testi ve Sperman korelasyon testi kullanılarak incelendi. $p<0.05$ olduğunda sonuçlar istatistiksel olarak anlamlı kabul edildi.

3. Bulgular

Çalışmaya dahil edilen 68 hastanın 32'sinde (%47,1) seminom, 36'sında (%52,9) non-seminom testis tümörü tespit edildi. Seminom grubunda yaş ortalaması 34,03±8,09, non-seminom grubunda 29,97±9,38 idi ve gruplar arasında anlamlı fark izlendi (p=0,02). En sık başvuru şikayeti, seminom ve non-seminom grubunda ele gelen kitle olarak saptandı (sırasıyla %34,4, %47,2), ve gruplar arasında anlamlı fark yoktu (p=0,2 hepsi >p=0,05). Seminom grubunun %59,4'ünde testis tümörü sağ tarafta, non-seminom grubunun %52,8'inde sol tarafta testis tümörü saptandı ve anlamlı fark izlenmedi (p=0,3 hepsi >p=0,05). Seminom grubunda radyolojik tümör boyutu 39,53±25,32 mm, patolojik tümör boyutu 45,34±22,76 mm, non-seminom grubunda radyolojik tümör boyutu 54,47±27,85 mm patolojik tümör boyutu ise 54,86±25,01 mm idi ve iki grup arasında anlamlı fark yoktu (sırasıyla p=0,06, p=0,1). Retroperitoneal LAP varlığı, T evresi, N evresi ve M evresi gruplar arasında benzerdi (sırasıyla; p=0,4, p=0,2, p=0,2, p=0,4) (Tablo 1).

Tümör belirteci olarak kullanılan AFP ve β-hCG değerleri non-seminom grubunda yüksek izlenirken, LDH değerlerinde gruplar arasında anlamlı fark izlenmedi (sırasıyla; p<0,001, p=0,04, p=0,2). Hematolojik parametreler incelendiğinde; lenfosit sayısı seminom grubunda 2,26±0,58 $\times 10^3/\mu L$ olarak saptanmış olup, non-seminom grubuna göre anlamlı yüksekti (p=0,020). WBC, MCV, MPV, PDW, nötrofil, monosit bazofil, eozinofil ve hemoglobin ve platelet değerleri her iki grupta benzerdi (hepsi p>0,05)

NLR, PLR, SII değerleri non-seminom grubunda, MPR değeri ise seminom grubunda yüksek izlenmiştir ve istatistiksel olarak gruplar arasında anlamlı fark saptandı (sırasıyla; p=0,03, p=0,004, p=0,01, p=0,04). MLR, SIRI ve AISI değerleri her iki grupta benzerdi (Tablo 2).

Tümör boyutu, TNM evresi, tümör belirteçleri ve hematolojik parametreler arasında yapılan korelasyon analizinde; tümör belirteçleri olarak kullanılan AFP, B-hCG ve LDH ile hematolojik parametreler arasında anlamlı bir korelasyon saptanmadı. Radyolojik tümör boyutu ile; AFP, B-hCG, LDH ve PLR arasında düşük-orta düzeyde pozitif bir korelasyon saptandı ve istatistiksel olarak anlamlıydı (sırasıyla; r=0,3 p=0,01, r=0,3 p=0,003, r=0,3 p=0,007, r=0,2 p=0,03). MPR ile tümör boyutu arasında ise orta düzeyde negatif bir korelasyon mevcuttu ve istatistiksel olarak anlamlıydı (r=0,3, p=0,005). T evresi ile MLR arasında düşük düzeyde pozitif bir korelasyon mevcuttu ve istatistiksel olarak anlamlıydı (r=0,2, p=0,02). Diğer belirteçlerin birbirleriyle olan korelasyonları tabloda belirtildi (Tablo 3).

Tablo 1. Grupların demografik ve klinik verilerinin karşılaştırılması

	Seminom group N= 32 n (%)	**Non-seminom group N=36 n (%)**	**p**
Yaş	34,03±8,09	29,97±9,38	**0,023**
Başvuru şikayeti			
Ele gelen kitle	11 (34,4)	17 (47,2)	0,265
Testiste ağrı	6 (18,8)	9 (25,0)	
Ağrısız şişlik	15 (46,9)	10 (27,8)	
Taraf			
Sağ	19 (59,4)	17 (47,2)	0,341
Sol	13 (40,6)	19 (52,8)	
Radyolojik tümör boyutu (mm)	39,53±25,32	54,47±27,85	0,062
Patolojik tümör boyutu (mm)	45,34±22,76	54,86±25,01	0,107
Retroperitoneal LAP			
Var	6 (18,8)	10 (27,8)	0,408
Yok	26 (81,3)	26 (72,2)	
T evresi			
1	18 (56,3)	18 (50)	0,273
2	12 (37,5)	11 (30,6)	
3	2 (6,3)	7 (19,4)	

N evresi			
0	26 (81,3)	23 (63,9)	
1	3 (9,4)	7 (19,4)	0,207
2	3 (9,4)	3 (8,3)	
3	0 (0)	3 (8,3)	
M evresi			
0	30 (93,8)	31 (86,1)	0,434
1a	2 (6,2)	5 (13,9)	

(LAP: lenfadenopati)

Tablo 2. Grupların tümör marker ve hematolojik verilerinin karşılaştırılması

	Seminom group N= 32	**Non-seminom group N=36**	**p**
AFP (ng/mL)	1,76 (1,38-2,26)*	12,94 (3,14-325,87)*	**<0,001**
LDH (U/L)	290 (218-495,75)*	376 (226-522,25)*	0,187
B-hCG (IU/L)	0,88 (0,20-5,39)*	4,96 (0,20-251,12)*	**0,040**
WBC ($\times10^3/\mu L$)	8,51±1,80	8,50±2,28	0,981
Nötrofil ($\times10^3/\mu L$)	5,38±1,76	5,75±2,22	0,383
Lenfosit ($\times10^3/\mu L$)	2,26±0,58	1,91±0,62	**0,020**
Monosit ($\times10^3/\mu L$)	0,66±0,17	0,61±0,62	0,240
Bazofil ($\times10^3/\mu L$)	0,03 (0,022-0,50)	0,03 (0,020-0,40)	0,566
Eozinofil ($\times10^3/\mu L$)	0,10 (0,090-0,195)	0,10 (0,052-0,297)	0,892
Hemoglobin (g/dL)	15,78±1,04	15,23±1,96	0,328
Platelet ($\times10^3/\mu L$)	251,21±55,71	272,72±68,68	0,217
MCV (fL)	86,82±5,19	86,05±6,73	0,606
MPV (fL)	9,73±1,18	9,78±1,30	0,865
PDW (fL)	12,88±2,57	12,50±2,76	0,672
NLR (%)	2,60±1,43	3,60±2,26	**0,030**
PLR (%)	120,14±49,04	164,81±115,78	**0,004**
MLR (%)	0,31±0,10	0,36±0,18	0,139
MPR (%)	0,0027±0,0009	0,0023±0,0006	**0,041**
SII ($\times10^3/\mu L$)	541,83 (373,34-800,83)	758,52 (529,48-1114,52)	**0,018**
SIRI ($\times10^3/\mu L$)	1,44 (1,12-2,09)	1,91 (1,29-2,58)	0,274
AISI ($\times10^6/\mu L^2$)	354,50 (209,73-495,82)	488,01 (278,09-739,53)	0,131

(:median (25-75 percentiles), AFP:alfa feto protein, B-hCG: beta-human koryonik gonadotropin, LDH;laktat dehidrogenaz, WBC: white blood cell, MCV: mean corpuscular volume, MPV: mean platelet volume, PDW: platelet distribution width, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, MPR: monocyte to platelet ratio, SII: systemic immune-inflammation index (neutrophil*platelet to lymphocyte ratio), SIRI: systemic inflammation response index (neutrophil* monocyte to lymphocyte ratio), AISI: aggregate index of systemic inflammation (neutrophil*platelet* monocyte to lymphocyte ratio))*

Tablo 3. Tümör boyutu, tümör markerları ve hematolojik parametrelerin korelasyon analizi

		Tümör boyutu (mm)	**T evresi**	**N evresi**	**M evresi**	**AFP**	**LDH**	**B-hCG**	**MPV**	**PDW**	**NLR**	**PLR**	**MLR**	**MPR**	**SII**	**SIRI**	**AISI**
Tümör boyutu (mm)	r																
	p																
T evresi	r	0,175															
	p	0,154															
N evresi	r	0,090	0,482														
	p	0,464	**<0,001**														
M evresi	r	-0,039	0,353	0,591													
	p	0,749	**0,003**	**<0,001**													
AFP	r	0,298	0,227	0,148	0,245												
	p	**0.014**	0,063	0,229	**0,044**												
LDH	r	0,323	0,236	0,153	0,259	0,278											
	p	**0,007**	0,053	0,213	**0,033**	**0,021**											
B-hCG	r	0,359	0,184	0,074	0,246	0,462	0,263										
	p	**0,003**	0,133	0,548	0,043	**<0,001**	**0,030**										
MPV	r	0,113	-0,146	0,084	-0,062	-0,031	-0,003	-0,050									

	p	0,359	0,235	0,494	0,617	0,800	0,984	0,684									
PDW	r	0,078	-0,213	-0,063	-0,035	0,094	-0,061	0,000	0,255								
	p	0,525	0,081	0,611	0,780	0,445	0,620	0,998	**0,036**								
NLR	r	0,116	0,118	0,009	-0,041	0,192	0,018	0,084	-0,007	-0,082							
	p	0,347	0,337	0,939	0,742	0,117	0,882	0,498	0,954	0,508							
PLR	r	0,255	0,157	0,169	0,041	0,222	0,223	0,030	-0,128	-0,356	0,534						
	p	**0,036**	0,202	0,167	0,742	0,068	0,068	0,806	0,298	0,508	**<0,001**						
MLR	r	0,113	0,277	0,144	0,102	0,103	0,231	0,090	-0,180	-0,223	0,556	0,672					
	p	0,359	**0,022**	0,243	0,406	0,403	0,058	0,465	0,142	0,068	**<0,001**	**<0,001**					
MPR	r	-0,337	0,029	-0,053	0,070	-0,219	-0,003	0,027	-0,058	0,166	-0,091	0,493	0,222				
	p	**0,005**	0,813	0,665	0,569	0,072	0,980	0,828	0,641	0,177	0,462	**<0,001**	0,069				
SII	r	0,154	0,114	-0,065	-0,063	0,167	0,096	0,061	-0,126	-0,196	0,796	0,798	0,672	-0,226			
	p	0,209	0,355	0,600	0,611	0,174	0,435	0,619	0,307	0,109	**<0,001**	**<0,001**	**<0,001**	0,064			
SIRI	r	0,014	0,173	-0,089	-0,046	0,047	0,076	0,098	-0,149	-0,093	0,767	0,508	0,821	0,279	0,836		
	p	0,907	0,159	0,469	0,712	0,705	0,536	0,428	0,225	0,448	**<0,001**	**<0,001**	**<0,001**	**0,021**	**<0,001**		
AISI	r	0,037	0,175	-0,082	-0,043	0,065	0,139	0,071	-0,217	-0,179	0,688	0,636	0,798	0,121	0,899	0,944	
	p	0,762	0,153	0,509	0,727	0,600	0,257	0,567	0,076	0,145	**<0,001**	<0,001	**<0,001**	0,326	**<0,001**	**<0,001**	

*(AFP:alfa feto protein, B-hCG: beta-human koryonik gonadotropin, LDH;laktat dehidrogenaz, MPV: mean platelet volume, PDW: platelet distribution width, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, MPR: monocyte to platelet ratio, SII: systemic immune-inflammation index (neutrophil*platelet to lymphocyte ratio), SIRI: systemic inflammation response index (neutrophil* monocyte to lymphocyte ratio), AISI: aggregate index of systemic inflammation (neutrophil*platelet* monocyte to lymphocyte ratio))*

4. Tartışma

Testis kanseri 40 yaş altı erkeklerde en sık görülen solid maliginite olmasına rağmen vakaların çoğunda kür sağlanabilmektedir (12). Olguların çoğunda (%90-95) germ hücreli tümör histolojisi izlenmektedir. Testis kanseri gelişiminde inmemiş testis, intratubuler germ hücreli neoplazi, genetik faktörler, moleküler faktörler ve çevresel faktörler suçlanmaktadır (4). İnflamasyonun tümör gelişimi, ilerlemesi, klinik görünümü ve prognozunda kritik bir rolü vardır ve çeşitli biyokimyasal ve hematolojik belirteçlerle ölçülebilir. Hematolojik parametrelerden türetilen inflamatuar indekslerin değerlendirmesinin avantajları; kolay ulaşılabilir olması ve maliyetinin düşük olmasıdır. Kansere bağlı periferik kan hücresi kompozisyonundaki değişiklikler genellikle miyeloid hücrelerin, yani nötrofil, monosit ve trombositlerin artması ve lenfositlerin azalması şeklinde ortaya çıkmaktadır (13).

Seminomlar genellikle ileri yaşta olmaktadır ve ilk başvuru yaşı ortalama 35'tir. Non-seminomatöz tümörler ise ortalama 25 yaş olmak üzere daha genç yaşta izlenmiştir (14). Richiardi ve arkadaşlarının ark. yaptığı bir çalışmada seminomlar ve non-seminomların pik yaptığı yaşlar arasında farklılık gözlenmiş; non-seminomatöz tümörlerin 30 yaşından önce, seminomların ise 30 yaşından sonra pik yaptığı görülmüştür (14). Benzer şekilde çalışmamızda seminom olguları daha ileri yaşlarda görülmüştür.

Non-seminomatöz tümörlerin yaklaşık %90'ında AFP veya β-hCG yükselmektedir. Seminomlarda ise %30'unda yükselmiş β-hCG değerleri saptanmaktadır ve AFP yükselmemektedir (15). Bizim çalışmamızda da benzer şekilde AFP ve β-hCG değerleri non-seminom grubunda daha yüksek tespit edilmiştir.

İnflamasyon, tümörün oluşmasından, ilerlemesine ve metastazına kadar çeşitli yollarla kanser gelişimi ve prognozunda önemli bir rol oynamaktadır. Periferik kanda artan nötrofil lenfosit oranı (NLR), çeşitli kanser türlerinde kötü prognostik belirteç olarak tanımlanmıştır (16). Lenfosit baskılanmasına yanıt olarak yükselen nötrofilin etkisi sonucu görülen yüksek NLR, antitümör bağışıklık yanıtını baskılayarak gelişen kanseri açıklayabilmektedir (17). Nötrofiller, makrofajlar ve diğer bazı hücrelerin vasküler endotelyal büyüme faktörü (VEGF), hepatosit büyüme faktörü (HGF), interlökin-6, interlökin-8 gibi tümör gelişimini destekleyen faktörleri salgıladığı bildirilmiştir. Ayrıca, bazı deneysel çalışmalar aktif nötrofillerin tümör gelişimini doğrudan ve dolaylı olarak uyarabileceğini göstermiştir (18, 19, 20).

Yüksel ve ark. WBC sayısının ve NLR'nin lokalize testis kanserinde basit bir tanı testi olarak kullanılabileceğini bildirmiştir (21). Başka bir çalışmada, ameliyat öncesi NLR ve lenfosit/monosit oranının testis tümörlerinin tanı ve takibinde mortalite oranlarını tahmin etmek için ucuz bir belirteç olarak kullanılabileceği gösterilmiştir (22).

Gökçen ve ark. tarafından yürütülen bir çalışmada, 36 testis tümörü olan hasta incelenmiş, NLR ve PLR değerleri testis tümörlerinde anlamlı olarak daha yüksek saptanmış ($p < 0,05$). Bizim çalışmamızda seminom ve non-seminomatöz testis tümörleri karşılaştırılmış olup NLR ve PLR değerleri non-seminomatöz testis tümörlerinde anlamlı derece yüksek saptanmıştır. ($p=0,03$). Tanı anında, seminomların %75-80'i evre 1, non-seminomatöz testis tümörlerinin ise %55-64'ü evre 1'dir (23). Non-seminomatöz testis tümörleri tanı anında daha ileri evrede olması ve NLR ve PLR'nin ileri evre ile ilişkili olması bu durumu açıklayabilir. Çalışmamızda ayrıca MPR düzeyleri değerlendirilmiş olup gruplar arasında istatistiksel olarak anlamlı fark saptanmıştır ve bizim bilgimize göre literatürde testis tümörlerinde MPR değerlendirilmemiştir.

Son zamanlarda, nötrofil, lenfosit ve platelet değerleri ile hesaplanabilen SII'nin ürolojik kanserlerde prognostik bir test olarak kullanılabilirliği araştırılmıştır (24). SII, immün yanıt ile inflamasyon arasındaki ilişkiyi yansıtır (25). Retrospektif bir çalışmada, testis tümörü evresini tahmin etmede, SII ve diğer hematolojik inflamatuar belirteçlerinin rolü araştırılmıştır. Bu çalışmada, yüksek SII değerlerinin ileri evre testis tümörü ile ilişkisi saptanmıştır (26). 833 testis tümörü hastasını içeren bir meta-analizde ise, yüksek SII düzeylerinin daha düşük genel sağkalım ve progresyonsuz sağkalım ile ilişkili bulunmuştur (27). Şimşekoğlu ve ark. ise yüksek SII değerlerinin non-seminomatöz testis tümörleri için bir belirteç olabileceğini belirtmiştir (28). 113 testis tümörü hastasının değerlendirildiği bir çalışmada; NLR, PLR, SII ve SIRI'nin ileri evre testis tümörlerinde istatistiksel olarak anlamlı ölçüde değiştiği gösterilmiştir (29). Bizim çalışmamızda da benzer şekilde non-seminomatöz testis tümörlerinde yüksek SII değerleri tespit edilmiş ve seminom grubu ile kıyaslandığında anlamlı fark saptanmıştır ($p=0,02$). SIRI değerleri seminom ve non-seminom grupları arasında benzer bulunmuştur. Yine bizim bilgimize göre literatürde değerlendirilmeyen AISI değeri değerlendirilmiştir ve gruplar arasında fark saptanmamıştır.

5. Sonuç

Tam kan sayımından türetilen inflamasyon indeksleri ek tetkik gerektirmeyen maliyet düşük, güvenilir ve kolayca erişilebilir parametrelerdir. Bu indeksler ameliyat önce germ hücreli testis tümörlerinin histolojik alt gruplarını öngörme ve patolojik tanıyı destekleme amacıyla kullanılabilir. Sistemik inflamasyon biyobelirteçleri ile germ hücreli testis tümörlerinin histolojik alt grupları arasındaki ilişkinin anlaşılabilmesi için daha geniş serilere ve uzun takip sürelerine sahip çalışmalara ihtiyaç vardır.

KAYNAKLAR

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30.
2. Park JS, Kim J, Elghiaty A, Ham WS. Recent global trends in testicular cancer incidence and mortality. Medicine (Baltimore). 2018;97(37):e12390.
3. Smith ZL, Werntz RP, Eggener SE. Testicular Cancer: Epidemiology, Diagnosis, and Management. Med Clin North Am. 2018;102(2):251-64.
4. De Toni L, Šabovic I, Cosci I, Ghezzi M, Foresta C, Garolla A. Testicular cancer: Genes, environment, hormones. Frontiers in endocrinology. 2019;10:408.
5. Germà-Lluch JR, Garcia del Muro X, Maroto P, Paz-Ares L, Arranz JA, Gumà J, et al. Clinical pattern and therapeutic results achieved in 1490 patients with germ-cell tumours of the testis: the experience of the Spanish Germ-Cell Cancer Group (GG). Eur Urol. 2002;42(6):553-62; discussion 62-3.
6. Beyer J, Albers P, Altena R, Aparicio J, Bokemeyer C, Busch J, et al. Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. Ann Oncol. 2013;24(4):878-88.
7. Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K, et al. Guidelines on Testicular Cancer: 2015 Update. Eur Urol. 2015;68(6):1054-68.
8. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454(7203):436-44.
9. Sfanos KS, Yegnasubramanian S, Nelson WG, De Marzo AM. The inflammatory microenvironment and microbiome in prostate cancer development. Nat Rev Urol. 2018;15(1):11-24.
10. Huszno J, Kołosza Z, Mrochem-Kwarciak J, Telka E, Jochymek B, Miszczyk L. Role of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio and platelets in

prognosis of patients with prostate cancer. Oncol Lett. 2022;24(3):305.
11. Moch H, Amin MB, Berney DM, Compérat EM, Gill AJ, Hartmann A, et al. The 2022 World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. Eur Urol. 2022;82(5):458-68.
12. Chung P, Warde P. Testicular cancer: germ cell tumours. BMJ Clin Evid. 2016;2016.
13. Sionov RV, Fridlender ZG, Granot Z. The Multifaceted Roles Neutrophils Play in the Tumor Microenvironment. Cancer Microenviron. 2015;8(3):125-58.
14. Vasdev N, Moon A, Thorpe AC. Classification, epidemiology and therapies for testicular germ cell tumours. Int J Dev Biol. 2013;57(2-4):133-9.
15. Dieckmann KP, Simonsen-Richter H, Kulejewski M, Anheuser P, Zecha H, Isbarn H, et al. Serum Tumour Markers in Testicular Germ Cell Tumours: Frequencies of Elevated Levels and Extents of Marker Elevation Are Significantly Associated with Clinical Parameters and with Response to Treatment. Biomed Res Int. 2019;2019:5030349.
16. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212-22.
17. Schaider H, Oka M, Bogenrieder T, Nesbit M, Satyamoorthy K, Berking C, et al. Differential response of primary and metastatic melanomas to neutrophils attracted by IL-8. Int J Cancer. 2003;103(3):335-43.
18. McCourt M, Wang J, Sookhai S, Redmond H. Proinflammatory Mediators Stimulate Neutrophil-Directed Angiogenesis. Archives of surgery (Chicago, Ill : 1960). 2000;134:1325-31; discussion 31.
19. Di Carlo E, Forni G, Musiani P. Neutrophils in the antitumoral immune response. Chem Immunol Allergy. 2003;83:182-203.
20. McCourt M, Wang JH, Sookhai S, Redmond HP. Activated human neutrophils release hepatocyte growth factor/scatter factor. Eur J Surg Oncol. 2001;27(4):396-403.
21. Yuksel OH, Verit A, Sahin A, Urkmez A, Uruc F. White blood cell counts and neutrophil to lymphocyte ratio in the diagnosis of testicular cancer: a simple secondary serum tumor marker. Int Braz J Urol. 2016;42(1):53-9.
22. Olcucu MT, Karamik K, Yilmaz K, Okuducu Y, Cakir S, Ates M. Preoperative Inflammation Markers and De Ritis Ratio in Predicting Clinical Presentation and Prognosis of Patients with Testicular Germ Cell Tumors. J Coll Physicians Surg Pak. 2020;30(10):1041-6.
23. Klepp O, Flodgren P, Maartman-Moe H, Lindholm CE, Unsgaard B, Teigum H, et al. Early clinical stages (CS1, CS1Mk+ and CS2A) of non-seminomatous testis cancer. Value of pre- and post-orchiectomy serum tumor marker information in prediction of retroperitoneal lymph node metastases. Swedish-Norwegian Testicular Cancer Project (SWENOTECA). Ann Oncol. 1990;1(4):281-8.
24. Wang S, Yang X, Yu Z, Du P, Cao Y, Ji Y, et al. The values of systemic immune-inflammation index and neutrophil-lymphocyte ratio in predicting testicular germ cell tumors: A retrospective clinical study. Front Oncol. 2022;12:893877.
25. Zhang Y, Lin S, Yang X, Wang R, Luo L. Prognostic value of pretreatment systemic immune-inflammation index in patients with gastrointestinal cancers. J Cell Physiol. 2019;234(5):5555-63.
26. Imamoglu GI, Eren T, Baylan B, Karacın C. May High Levels of Systemic Immune-Inflammation Index and Hematologic Inflammation Markers Suggest a Further Stage in Testicular Tumours? Urol Int. 2019;103(3):303-10.
27. Salazar-Valdivia FE, Valdez-Cornejo VA, Ulloque-Badaracco JR, Hernandez-Bustamante EA, Alarcón-Braga EA, Mosquera-Rojas MD, et al. Systemic Immune-Inflammation Index and Mortality in Testicular Cancer: A Systematic Review and Meta-Analysis. Diagnostics (Basel). 2023;13(5).
28. Şimşekoğlu MF, Vural A, Macit M, Yıldız F, Kalender G, Aferin U, et al. The clinical value of complete blood count-based immun parameter in predicting testicular cancer pathology and prognosis. Anatolian Clinic the Journal of Medical Sciences. 2024;29(2):210-6.
29. Bumbasirevic U, Bojanic N, Simic T, Milojevic B, Zivkovic M, Kosanovic T, et al. Interplay between Comprehensive Inflammation Indices and Redox Biomarkers in Testicular Germ-Cell Tumors. J Pers Med. 2022;12(5).

Osmangazi Journal of Med, 2025;47(1):140-145
DOI: 10.20515/otd.1586027

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Prognostik Nutrisyonel İndeks Jüvenil İdiyopatik Artritte Prognostik Biyobelirteç Olabilir Mi?

Is the Prognostic Nutritional Index A Potential Prognostic Biomarker in Juvenile Idiopathic Arthritis?

Emine Nur Sunar Yayla, Elif Arslanoğlu Aydin, Bahar Demirbaş, Ezgi Yilmazer Yönder, Esra Bağlan, Semanur Özdel

Etlik Şehir Hastanesi, Çocuk Romatoloji Kliniği, Ankara, Türkiye

ORCID ID of the authors
ENSY. 0000-0003-1646-2341
EAA. 0000-0002-1287-4683
BD. 0009-0008-6528-4813
EYY. 0000-0003-3311-4947
EB. 0000-0001-5637-8553
SÖ. 0000-0001-5602-4595

Correspondence / Sorumlu yazar:
Emine Nur SUNAR YAYLA

Etlik Şehir Hastanesi, Çocuk Romatoloji Kliniği, Ankara, Türkiye

e-mail: enursunar@hotmail.com

Abstract: This study explores the relationship between disease activity and the prognostic nutritional index (PNI) in patients with juvenile idiopathic arthritis (JIA) and aims to assess the potential of PNI as a prognostic biomarker in JIA.Patients diagnosed with oligoarticular and polyarticular JIA were categorized into two groups based on the Juvenile Arthritis Disease Activity Score (JADAS): those in remission or with low disease activity, and those with moderate to high disease activity. Demographic, clinical, and laboratory characteristics, along with PNI values, were compared between the two groups.The study included 106 patients with oligoarticular and polyarticular JIA, with a median age of 5.95 years and 67(63.2%) were female. Uveitis was observed in 18 patients (17%) and family history in 14 patients (13.2%).. Approximately two-thirds (n=69) were diagnosed with oligoarticular JIA, while 33.1% (n=35) had polyarticular JIA. Based on JADAS scores at the 12-month follow-up, two groups emerged: Group 1, with patients in remission or with low disease activity, and Group 2, with patients experiencing moderate to high disease activity. Corticosteroid treatment was administered to 52 patients (58.4%) in group 1 and 16 patients (94.1%) in group 2. The use of biologic DMARDs was significantly higher in group 2 and etanercept was the most preferred agent. Biologic DMARDs were changed in 9 patients (11.4%), while 15 patients (14.2%) achieved remission without treatment. The median PNI value did not differ significantly between the groups.PNI does not adequately reflect disease activity in JIA and should not be considered a reliable prognostic tool for this patient population.
Keywords: Juvenile idiopathic arthritis, prognosis, prognostic nutritional index

Etik Kurul Onayı: Çalışma Ankara Etlik Şehir Hastanesi Bilimsel Araştırmalar Etik Kurulu tarafından onaylanmıştır. Karar no: AEŞH-BADEK-2024-922 Tarih: 16.10.2024
Telif Hakkı Devir Formu: Tüm yazarlar tarafından Telif Hakkı Devir Formu imzalanmıştır.
Yazar Katkısı: Veri toplanması; ENSY, EAA, BD, EYY, Verilerin analizi; ENSY, EAA; Yazım; ENSY, Literatür taraması ve düzenleme; SÖ, EB
Çıkar Çatışması Beyanı: Yazarlar arasında herhangi bir çıkar çatışması bulunmamaktadır.
Destek ve Teşekkür Beyanı: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Özet: Bu çalışma, jüvenil idiyopatik artrit (JİA) hastalarında hastalık aktivitesi ile prognostik nutrisyonel indeks (PNI) arasındaki ilişkiyi incelemeyi amaçlamaktadır. Ayrıca, PNI'nın JİA'da prognostik bir biyobelirteç olarak kullanılabilirliğini değerlendirmek hedeflenmiştir. Oligoartiküler ve poliartiküler JİA tanısı alan hastalar, Jüvenil Artrit Hastalık Aktivite Skoru (JADAS) ölçümüne göre remisyon ve düşük hastalık aktivitesine sahip olanlar ile orta ve yüksek hastalık aktivitesi gösterenler olmak üzere iki gruba ayrıldı. İki grup arasında demografik, klinik ve laboratuvar özellikler ile PNI değerleri karşılaştırıldı. Çalışmaya, oligoartiküler ve poliartiküler JİA tanılı 106 hasta dahil edildi. Hastaların ortanca yaşı 5,95 yıl olup, 67'si (%63,2) kızdır. Üveit 18 hastada (%17), aile öyküsü ise 14 hastada (%13,2) gözlenmiştir. Hastaların üçte ikisi (n=69) oligoartiküler, %33,1'i (n=35) poliartiküler JİA tanısına sahiptir. On ikinci ay JADAS skoruna göre, remisyon/düşük hastalık aktivitesindeki hastalar (Grup 1) ile orta/yüksek hastalık aktivitesindeki hastalar (Grup 2) olarak iki grup oluşturulmuştur. Grup 1'de 52 hastaya (%58,4), grup 2'de ise 16 hastaya (%94,1) kortikosteroid tedavisi uygulanmıştır. Biyolojik DMARD kullanımı ise grup 2'de anlamlı derecede yüksektir ve en sık tercih edilen ajan etanersepttir. Hastaların 9'unda (%11,4) biyolojik DMARD değişikliği yapılırken, 15'inde (%14,2) tedavisiz remisyon sağlanmıştır. Ortanca PNI değeri gruplar arasında anlamlı fark göstermemiştir.PNI, JİA'lı hastalarda hastalık aktivitesini yansıtmakta yetersiz kalmaktadır ve prognoz tahmininde kullanışsız bir parametredir.
Anahtar Kelimeler: Jüvenil idiyopatik artrit, prognoz, prognostik nutrisyonel indeks

Received : 18.10.2024
Accepted : 13.01.2025
Published : 14.01.2025

How to cite/ Atıf için: Sunar Yayla, EN Arslanoğlu Aydin E, Demirbaş B, Yilmazer Yönder E, Bağlan E, Özdel S. Prognostik Nutrisyonel İndeks Jüvenil İdiyopatik Artritte Prognostik Biyobelirteç Olabilir Mi, Osmangazi Journal of Medicine, 2025;47(1):140-145

1. Giriş

Jüvenil idiyopatik artrit (JİA), uzun süreli sinovyal inflamasyon ile karakterize, eklem yapısında hasara neden olabilen kronik otoimmün bir hastalıktır (1). Eklem hasarının yanı sıra göz ve böbrek gibi organlarda geri dönüşsüz hasara yol açabilir (2). Bu morbiditeler, hastanın yaşam kalitesini olumsuz etkileyebilir. Bu nedenle, tedavi yanıtını izlemek ve hastalık aktivitesini belirlemek oldukça önemlidir (3). JİA'da hastalık aktivite indeksi olan Jüvenil Artrit Hastalık Aktivite Skoru (JADAS) ilk kez 2009'da geliştirilmiş olup, hasta muayene bulgularını, genel sağlık durumunu, eritrosit sedimentasyon hızı (ESH) ve C-reaktif protein (CRP) düzeylerini içermektedir (4).

Hastalık aktivitesini gösterdiği düşünülen bir diğer parametre prognostik nutrisyonel indeks (PNI)'dir. PNI, ilk kez beslenme yetersizliği olan gastrointestinal kanser hastalarında kötü prognozu tahmin etmek için kullanılmıştır. PNI, periferik dolaşımdaki lenfosit sayısı ve serum albümin düzeyine dayalı olarak hesaplanmaktadır (5). Albumin inflamasyon sırasında negatif akut faz reaktanıdır ve bu nedenle serum albumin seviyesi, inflamatuar yük ile ters orantılı olarak değişebilir (6). Lenfosit sayısı ise romatoid artrit ve sistemik lupus eritematozus gibi otoimmün hastalıklarda azalabilir (7). Sistemik immun-inflamasyon indeksi olan PNI, son yıllarda bazı romatolojik ve diğer kronik hastalıklarda inflamasyon göstergesi olarak araştırılmış ve hastalık aktivitesi ile ilişkili bulunmuştur (8-10).

Bu araştırmanın amacı, JİA hastalarında hastalık aktivitesi ile PNI arasındaki ilişkinin incelenmesi ve PNI'nın JİA'da prognostik bir biyobelirteç olarak kullanılabilirliğinin değerlendirilmesidir.

2. Gereç ve Yöntem

2.1 .Hastalar ve Çalışma Tasarımı

Ekim 2022 ile Temmuz 2024 tarihleri arasında, Ankara Etlik Şehir Hastanesi Çocuk Romatoloji Kliniği'nde ILAR (International League of Associations for Rheumatology) kriterlerine göre (11) oligoartiküler ve poliartiküler JİA tanısı konulan 0-18 yaş arasındaki 106 çocuk hasta çalışmaya dahil edildi. Akut enfeksiyonlar, hematolojik hastalıklar, kronik karaciğer ve böbrek yetmezliği, otoimmün ve otoinflamatuvar hastalıkları olan hastalar ise çalışma dışı bırakıldı. Veriler, hastaların tıbbi kayıtlarından elde edildi. Kaydedilen bilgiler arasında hasta demografisi (yaş, cinsiyet), klinik bulgular, semptom süresi, JİA alt tipi (oligoartiküler veya poliartiküler), komplikasyonlar, ilaç öyküsü, tanı sırasındaki laboratuvar bulguları (tam kan sayımı, CRP, ESH, antinükleer antikorlar [ANA], romatoid faktör, HLA-B27), uygulanan tedaviler ve hastalık aktivitesinin tanı anında ve 12 ay sonra JADAS 27 ile yapılan değerlendirmesi yer almaktadır.

2.2. Hastalık aktivitesi ve PNI'nın değerlendirilmesi

Hastalık aktivitesinin takibinde klinik ve laboratuvar değerlendirmeleri içeren JADAS kullanılmıştır. JADAS, şu şekilde hesaplanmıştır: 1**.** Hekimin hastalık aktivitesine yönelik genel değerlendirmesi (10 cm'lik bir VAS üzerinde 0, hiçbir aktiviteyi ve 10, maksimum aktiviteyi temsil eder); 2. Ebeveynin çocuğun genel durumu üzerine değerlendirmesi (0-10 VAS üzerinde); 3. Aktif eklem sayısı (71, 27 veya 10 eklem); 4. ESH (mm/saat)-20/10 veya CRP (mg/L)-10/10 (4).

JADAS 27 eklemde hesaplandı. JADAS'a göre 0-1 puan arası remisyon, 1-10 puan arası düşük hastalık aktivitesi, 10-25 puan arası orta hastalık aktivitesi ve 25 puan üzeri yüksek hastalık aktivitesi olarak kabul edildi (12). Hastalar, remisyon ve düşük hastalık aktivitesine sahip olanlar ile orta ve yüksek hastalık aktivitesi gösterenler olmak üzere iki gruba ayrıldı.

PNI tanı anındaki serum albümin değerinin (g/dL) on katı ile periferik lenfosit sayısının (/mm3) 0,005 ile çarpımının toplamı olarak hesaplandı (5).

2.3. İstatiksel Analiz

İstatistiksel analizler SPSS versiyon 26.0 istatistik yazılımı (IBM, Şikago, A.B.D.) kullanılarak yapıldı. Kantitatif veriler için, verilerin normal dağılıp dağılmadığı Kolmogorov–Smirnov testi ve histogram analizleri ile görsel olarak değerlendirildi. Kantitatif veriler ortanca ve çeyrekler arası aralık (ÇAA) ile ifade edildi ve iki grup karşılaştırılırken Mann Whitney U testi kullanıldı. Kategorik veriler sayı ve yüzde olarak sunuldu. İki grup arasında kategorik veriler karşılaştırılırken Ki-kare ya da Fisher's exact testten uygun olanı kullanıldı. $p<0,05$ istatistiksel olarak anlamlı kabul edildi. Korelasyon analizlerinde Spearman yöntemi kullanılarak analizler gerçekleştirildi.

Etik Kurul İzni

16.10.2024 tarihinde hastanemiz etik kurulundan 2024-922 karar numarası ile onay alınmış olup, çalışma Helsinki Deklarasyonu ilkelerine uygun şekilde yürütülmüştür. Tüm yazarlar tarafından Telif Hakkı Devir Formu imzalanmıştır. Retrospektif bir tasarıma sahip olduğu için hastalardan imzalı onam alınmamıştır.

3. Bulgular

Çalışmaya oligoartiküler ve poliartiküler jüvenil idiyopatik artrit (JİA) tanısı alan 106 hasta dahil edilmiştir. Hastaların ortanca yaşı 5,95 yıl (ÇAA:7,12), 67'si (%63,2) kız , 39'u (%36,8) erkektir.. Üveit eşlik eden 18 hasta (%17), aile öyküsü olan 14 hasta (%13,2) mevcuttur. JİA tipleri açısından değerlendirildiğinde, hastaların yaklaşık üçte ikisi (n=69) oligoartiküler JİA, %33,1'i (n=35) ise poliartiküler JİA tanısı almıştır. Tanı anındaki JADAS27'nin median değeri 16,3 (ÇAA: 8) olarak saptandı. JADAS27 ile PNI arasında negatif yönde ve düşük düzeyde bir korelasyon bulundu (Rho: -0,193, p = 0,046). Hastalar, 12.aydaki JADAS ölçümüne göre remisyon veya düşük hastalık aktivitesine sahip olanlar (Grup 1) ve orta veya yüksek hastalık aktivitesi gösterenler (Grup 2) olmak üzere iki gruba ayrılmıştır. Demografik ve klinik veriler Tablo 1'de özetlenmiştir.

Tedavi yöntemleri açısından, Grup 1'deki hastaların 52'sine (%58,4) kortikosteroid tedavisi uygulanırken, Grup 2'de 16 hastaya (%94,1) uygulanmıştır (p=0,005). Biyolojik DMARD kullanımının Grup 2'de daha sık olduğu gözlemlenmiştir (p=0,038). En sık kullanılan biyolojik ajan olan etanersept, orta veya yüksek hastalık aktivitesi bulunan grup 2'de 14 hastada (%82,4) tercih edilmiştir (p=0,01). Diğer sık kullanılan bDMARD'lar ise sırasıyla adalimumab, tosilizumab, infliksimab ve tofasitinib olmuştur.

Prognoz açısından bakıldığında, biyolojik DMARD değişimi hastaların 9'unda (%11,4)gerçekleştirilmiş olup 15 hastada (%14,2) tedavisiz remisyon sağlanmıştır. Relaps 22 hastada (%20,8) saptanmış ancak bu oranlar arasında gruplar arası istatistiksel anlamlı bir fark görülmemiştir (p=0,076, p=0,456, p>0,999).

Tanı anında ortanca PNI değeri (ÇAA) Grup 1'de 56,85 (8.53) olarak hesaplanmış ve diğer grupla anlamlı bir fark göstermemiştir (p=0,541).

Tablo.1 Jüvenil idiyopatik artritli hastaların JADAS27 ile belirlenen hastalık aktivitesine göre demografik, klinik ve laboratuvar özellikleri

	Tüm hastalar n=106	**JADAS27 (12.ay) n=89 Remisyon-düşük hastalık aktivitesi**	**JADAS 27 (12.ay) n=17 Orta-yüksek hastalık aktivitesi**	***p* değeri**
Yaş, yıl; ortanca (ÇAA)	5,95 (7,12)	4,96 (6,2)	9,96 (10,67)	0,230
Kız cinsiyet, n (%)	67 (63,2)	55 (61,8)	12 (70,6)	0,491
Üveit varlığı, n (%)	18 (17)	14 (15,7)	4 (23,5)	
Aile öyküsü, n (%)	14 (13,2)	11(12,4)	3 (17,6)	0,695
ANA pozitifliği, n (%)	38 (35,8)	32 (36)	6 (35,3)	0,958
Lenfosit (mcL, ortanca)	2765 (1715)	2740 (1710)	2760 (1510)	0,516
Albumin (g/dL, ortanca)	4,3 (0,6)	4,3 (0,6)	4,2 (0,85)	0,876
JİA tipi				
Oligoartüküler JİA, n (%)	69 (65,1)	60 (67,4)	9 (52,9)	0,251
Uzamış oligoartiküler JİA, n (%)	2 (1,9)	2 (2,2)	0	>0,999
RF+ poliartiküler JİA, n (%)	6 (5,7)	5 (5,6)	1 (5,9)	>0,999
RF- poliartiküler JİA, n (%)	29 (27,4)	22 (24,7)	7 (41,2)	0,233
Tedaviler				
KS, n (%)	68 (64,2)	52 (58,4)	16 (94,1)	**0,005**
İAS, n (%)	45 (42,5)	39 (43,8)	6 (35,3)	0,515
MTX, n (%)	104 (98,1)	88 (98,9)	16 (94,1)	0,296
Leflunomid, n (%)	6 (5,7)	4 (4,5)	2 (11,8)	0,246
Salazoprin, n (%)	1 (0,9)	1 (1,1)	0	>0,999
bDMARD kullanımı, n (%)	78 (73,6)	62 (69,7)	16 (94,1)	**0,038**

Etanersept, n (%)	57 (53,8)	43 (48,3)	14 (82,4)	**0,01**
Adalimumab, n (%)	26 (24,5)	20 (22,5)	6 (35,3)	0,355
Tosilizumab, n (%)	6 (5,7)	4 (4,5)	2 (11,8)	0,246
İnfliksimab, n (%)	3 (2,8)	2 (2,2)	1 (5,9)	0,411
Tofasitinib, n (%)	1 (0,9)	1 (1,1)	0	>0,999
Prognoz				
bDMARD değişimi, n (%)	9 (11,4)	5 (7,9)	4 (25)	0,076
İlaçsız remisyon, n (%)	15 (14,2)	14 (15,7)	1 (5,9)	0,456
Relaps, n (%)	22 (20,8)	19 (21,3)	3 (17,6)	>0,999
PNI, ortanca (ÇAA)	57 (8,7)	56,85 (8,53)	58 (8,6)	0,541

ANA, Antinükleer antikor; bDMARD, Biyolojik DMARD; PNI, Prognostik nutrisyonel indeks; KS, Kortikosteroid; İAS, İntraartiküler steroid; JADAS, Jüvenil Artrit Hastalık Aktivite Skoru; JİA, Jüvenil idiyopatik Artrit; MTX, Metotreksat; RF, Romatoid Faktör

4. Tartışma ve Sonuç

PNI, ilk olarak Onodera ve ark. tarafından gastrointestinal cerrahi geçiren hastalarda ameliyat sonrası komplikasyon riskini öngörmek amacıyla kullanılan parametre olarak tanımlanmıştır (5). Ancak son yıllarda, PNI'nın malignite ve kronik hastalıklarda prognoz ile ilişkili olduğunu gösteren çok sayıda çalışma bulunmaktadır (6). Bu çalışmada, JİA hastalarında PNI ile hastalık aktivitesi arasındaki ilişkiyi değerlendirdik. Aktif ve inaktif JİA hastaları karşılaştırıldığında, PNI değerleri açısından iki grup arasında anlamlı bir fark bulunmamıştır.

PNI'nın çocukluk çağı kronik hastalıklarda prognostik araç olarak kullanılabilirliğinin gösterildiği hastalıklardan birisi Kawasaki hastalığıdır (13). Kawasaki hastalığı, çocuklarda görülen ve akut inflamatuar bir süreç olan orta damar vaskülitidir. İnflamasyon sonucunda damar duvarlarında hasar oluşur ve bu durum çeşitli proteinlerin, özellikle de albuminin, damar dışına sızmasına neden olur. Ayrıca, inflamasyon sırasında vücutta yaygın protein kaybı ve karaciğer işlevlerinin değişmesi de albumin düşüklüğüne katkıda bulunabilir. Bu nedenle Kawasaki hastalığında serum albumin düzeyleri düşebilir (14). JİA ise kronik bir inflamatuar eklem hastalığıdır (7). JİA'da inflamasyon daha sınırlı olabilir ve damar duvarlarında Kawasakihastalığında olduğu gibi yaygın hasar gelişmez. Ayrıca, JİA'da inflamasyon süreci daha uzun ve yavaş bir seyir izlediğinden protein kaybı belirgin olmayabilir. Bu nedenle JİA'da albumin düzeyleri genellikle normal kalır ya da daha az etkilenir. Bu durum, JİA hastalarında hastalık aktivitesi ile PNI'nın değişiklik göstermemesinin nedenlerinden biri olabilir.

Öz ve ark.'nın 138 romatoid artrit (RA) hastası üzerinde yaptığı araştırmada, hastalık aktivitesi yüksek olan RA'lı hastalarda PNI düzeyinin düşük olduğu belirlenmiş ve PNI'nın RA'da hastalık aktivitesini öngörmede kullanılabileceği gösterilmiştir (9). RA, JİA gibi kronik inflamatuar bir hastalık olmakla birlikte, aralarında patofizyolojik açıdan farklılıklar bulunmaktadır. RA, erişkin yaş grubunda görüldüğünden hastalık süresi daha uzun olabilir ve daha şiddetli kronik inflamasyon ortaya çıkabilir. Kronik inflamasyon, katabolik bir durum yaratarak beslenme durumunu daha fazla etkileyebilir ve prognoz üzerinde olumsuz bir etkiye neden olabilir (15, 16). JİA'lı çocuklar ise büyüme evresinde olduklarından vücutlarının beslenme ihtiyaçları ve metabolik yanıtları farklı olabilir; ayrıca büyüme ve gelişim süreçleri inflamatuar süreçleri telafi edebilecek düzeyde olabilir. Bu nedenle, JİA'da beslenme indeksi her zaman düşük olmayabilir.

PNI'nın hastalık aktivitesini ölçmede kullanışlı olduğunu gösteren bir diğer çalışma Ahn ve ark. tarafından ANCA ilişkili vaskülit (AAV) hastalarında yapılmıştır. Bu çalışmada, AAV hastalarında hastalık aktivitesi ile PNI arasında negatif korelasyon saptanmış ve bu durum hipoalbuminemi ve lenfopeniye bağlanmıştır. Hipoalbuminemi, diğer inflamatuar hastalıklarda olduğu gibi malnutrisyon, proteinüri ve sistemik inflamasyon ile ilişkilendirilmiştir (6). Ayrıca, AAV hastalarında lenfosit sayısının, periferik T hücrelerinin etkilenen dokuya invazyonu nedeniyle azaldığı bildirilmiştir (17, 18).

Behçet hastalarında yapılan ve PNI'nın değerlendirildiği bir başka çalışmada ise, nötrofil sayısının aktif Behçet hastalığı grubunda yüksek lenfosit sayısının ise düşük saptandığı bildirilmiştir (10). Nötrofiller, doğuştan gelen bağışıklık sisteminin önemli bileşenleridir. Behçet hastalığındaki kronik inflamasyon nedeniyle birçok proinflamatuar ve/veya inflamatauar sitokin üretilir ve nötrofillerin aktivasyonu sağlanır (19, 20). Aktive olmuş nötrofiller, Behçet hastalığında doku hasarı

sürecinde rol oynar. Aktif hastalıktaki enflamatuvar durum, lenfositlerin apoptozunun düzensizleşmesine neden olabilir ve sonuç olarak lenfosit üretiminde azalma görülebilir (21).

Diğer kronik inflamatuar hastalıklarda olduğu gibi, JİA'da da T ve B lenfositler, inflamatuvar süreçlere katılmak üzere dokulara yönelir. Bu durum, dolaşımdaki lenfosit sayısının azalmasına yol açabilir. Ayrıca, inflamatuar süreçler lenfositlerin apoptozunu artırarak veya lenfosit üretiminde azalmaya yol açarak lenfopeniye neden olabilir. Ancak JİA'da inflamasyon daha çok eklem dokularını etkilediğinden, bağışıklık hücrelerinin aşırı tüketiminden ziyade lokal doku hasarı görülür. Bu nedenle, diğer otoimmün hastalıklardan farklı olarak, JİA'da dolaşımdaki lenfosit sayısı sıklıkla korunur (7). Donato ve ark.'nın çalışmasında JİA hastalarında CRP/albumin oranının hastalık aktivitesi ile ilişkisi araştırılmıştır. CRP/albumin oranı ile JADAS27 arasında pozitif korelasyon saptanmamıştır (22). Bizim hasta grubumuzda da hem lenfosit sayısında hem de albumin düzeyinde anlamlı bir azalma gözlemlenmemiştir. Bu nedenle PNI, JİA'lı hastalarda hastalık aktivitesi ile ilişkili bulunmamıştır. Çalışmamızın tek merkezli ve retrospektif tasarımlı olması gibi bazı kısıtlamaları bulunsa da, PNI'nın daha önce JİA'li hastalarda araştırılmamış olması çalışmamızın güçlü yanlarındandır.

PNI, Kawasaki hastalığı, RA, AAV, Behçet hastalığı gibi birçok romatolojik hastalıkta hastalık aktivitesi ile ilişkili olup, prognozu öngörmede kullanılabilirken, JİA'lı hastalarda hastalık aktivitesini yansıtmayan ve prognozu öngörmede kullanışlı olmayan bir parametredir.

KAYNAKLAR

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007;369(9563):767-78.
2. Viola S, Felici E, Magni-Manzoni S, Pistorio A, Buoncompagni A, Ruperto N, et al. Development and validation of a clinical index for assessment of long-term damage in juvenile idiopathic arthritis. Arthritis Rheum. 2005;52(7):2092-102.
3. Passo MH, Taylor J. Quality improvement in pediatric rheumatology: what do we need to do? Curr Opin Rheumatol. 2008;20(5):625-30.
4. Consolaro A, Giancane G, Schiappapietra B, Davì S, Calandra S, Lanni S, et al. Clinical outcome measures in juvenile idiopathic arthritis. Pediatric Rheumatology. 2016;14:1-8.
5. Onodera T, Goseki N, Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. Nihon Geka Gakkai Zasshi. 1984;85(9):1001-5.
6. Ahn SS, Jung SM, Song JJ, Park YB, Lee SW. Prognostic nutritional index is associated with disease severity and relapse in ANCA-associated vasculitis. Int J Rheum Dis. 2019;22(5):797-804.
7. Zaripova LN, Midgley A, Christmas SE, Beresford MW, Baildam EM, Oldershaw RA. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. Pediatr Rheumatol Online J. 2021;19(1):135.
8. Seo M, Yamada T, Morita T, Furukawa Y, Tamaki S, Iwasaki Y, et al., editors. Prognostic value of systemic immune-inflammation index in patients with chronic heart failure. European Heart Journal; 2018: Oxford Unıv Press Great Clarendon St, Oxford Ox2 6dp, England.
9. Öz N, Gezer HH, Cilli Hayıroğlu S, Duruöz MT. Evaluation of the prognostic nutritional index (PNI) as a tool for assessing disease activity in rheumatoid arthritis patients. Clinical Rheumatology. 2024;43(5):1461-7.
10. Ataş N, Babaoğlu H, Demirel E, Çelik B, Salman RB, Satış H, et al. Use of prognostic nutritional index in the evaluation of disease activity in patients with Behçet's disease. European Journal of Rheumatology. 2020;7(3):99.
11. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. The Journal of rheumatology. 2004;31(2):390-2.
12. Başaran Ö, Aydın F, Çakar N, Uncu N, Bal A, Kızılgün M, et al. Oligoartiküler juvenil idiopatik artrit hastalarının aktif ve inaktif dönemdeki sitokin düzeylerinin değerlendirilmesi. Turkish Journal of Pediatric Disease. 2019;13(4):252-7.
13. Liu J, Ye B, Su D, Qin S, Zhao W, Pang Y. Evaluation of laboratory predictors for intravenous immunoglobulin resistance and coronary artery aneurysm in Kawasaki Disease before and after therapy. Clinical Rheumatology. 2023;42(1):167-77.

14. Terai M, Honda T, Yasukawa K, Higashi K, Hamada H, Kohno Y. Prognostic impact of vascular leakage in acute Kawasaki disease. Circulation. 2003;108(3):325-30.
15. Wunder A, Muller-Ladner U, Stelzer E, Neumann E, Sinn H, Gay S, et al. Albumin-based drug delivery as novel therapeutic approach for rheumatoid arthritis. Arthritis Res Ther. 2003;5:1-54.
16. Levick JR. Permeability of rheumatoid and normal human synovium to specific plasma proteins. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1981;24(12):1550-60.
17. Schulze-Koops H. Lymphopenia and autoimmune diseases. Arthritis Res Ther. 2004;6:1-3.
18. Berden AE, Kallenberg C, Savage C, Yard BA, Abdulahad WH, De Heer E, et al. Cellular immunity in Wegener's granulomatosis: characterizing T lymphocytes. Arthritis & Rheumatism. 2009;60(6):1578-87.
19. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. New England Journal of Medicine. 1999;341(17):1284-91.
20. Selders GS, Fetz AE, Radic MZ, Bowlin GL. An overview of the role of neutrophils in innate immunity, inflammation and host-biomaterial integration. Regenerative biomaterials. 2017;4(1):55-68.
21. Kam P, Ferch N. Apoptosis: mechanisms and clinical implications. Anaesthesia. 2000;55(11):1081-93.
22. Di Donato G, Attanasi M, Mariarita d' Angelo D, La Bella S, Di Ludovico A, Chiarelli F, et al. Associations of C reactive protein to albumin ratio, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio with disease activity in patients with juvenile idiopathic arthritis. BMC Rheumatol. 2024;8(1):26.

Research Article / Araştırma Makalesi

Forensic Medical Evaluation of Non-Fatal Traumatic Head Bone Fractures

Ölümle Sonuçlanmayan Travmatik Kafa Kemik Kırıklarının Adli Tıbbi Değerlendirilmesi

[1]Ümit Şimşek, [1]Bahadır Saka, [1]Tuğrul Kılıboz, [1]Neslihan Polat, [2]Ömer Seyda Köse, [1]Kenan Karbeyaz

[1]Eskişehir Osmangazi University Faculty of Medicine, Department of Forensic Medicine, Eskişehir, Türkiye
[2]Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Forensic Medicine, Çanakkale, Türkiye

Abstract: Head bone fractures are encountered in forensic medicine practice due to their origin. In the present study, we aimed to evaluate the demographic data, injury characteristics, clinical findings accompanying bone fractures and forensic reports of cases with skull fractures and to share them with the literature. In this study, cases with non-fatal traumatic skull fractures that did not result in death admitted to our department during the 10-year period between 01.01.2014 and 31.12.2023 were included in the study. Hospital documents and investigation documents of the cases were retrospectively analyzed. It was determined that 75.6% of the cases were male and the mean age was 37±9.6 years. It was determined that 56.2% of the skull fractures occurred as a result of traffic accidents, the most common fracture was the frontal bone (n=206, 53.4%) and 54.1% of the cases were linear fractures. In our study, it was determined that skull fractures were most common in males, in the young adult age group, most commonly due to traffic accidents, and in the form of linear fractures in the frontal bone. The findings were consistent with the literature. When preparing a forensic report on skull fractures, the location of the fracture, the type of fracture and the number of fractures are important in terms of determining the life threat and the effect of the fracture on life functions.
Keywords: head bone fracture, forensıc report, traflc accıdent, forensıc medıcıne

Özet: Kafa kemik kırıkları, orijinleri gereği, adli tıp pratiğinde karşılaşılabilen olgulardır. Sunulan çalışmada, kafa kemik kırıklı olgulara ait demografik verilerin, yaralanma özelliklerinin, kemik kırığına eşlik eden klinik bulguların ve olguların adli raporlarının değerlendirilmesi ve litaretürle paylaşılması amaçlanmıştır. Çalışmada, 01.01. 2014- 31.12.2023 tarihleri arasındaki 10 senelik zaman dilimde, Anabilim Dalımıza başvuran ölümle sonuçlanmayan travmatik kafa kemik kırıklı olgular çalışmaya dahil edilmiştir. Olgulara ait, hastane evrakları, soruşturma evrakları retrospektif olarak incelenmiştir. Olguların, % 75,6'sının erkek olduğu, yaş ortalamasının 37±9,6 olduğu belirlenmiştir. Kafa kemik kırıklarının % 56,2'sinin trafik kazası sonucu meydana geldiği, en sık frontal kemiğin kırıldığı (n=206, % 53,4), olguların % 54,1'inin lineer kırık şeklinde olduğu belirlenmiştir. Çalışmamızda, kafa kemik kırıklarının en sık erkeklerde, genç erişkin yaş grubunda, en sık trafik kazası nedeniyle, frontal kemikte lineer kırık şeklinde olduğu belirlenmiştir. Elde edilen bulgular literatürle uyumlu bulunmuştur. Kafa kemik kırıkları ile ilgili adli rapor düzenlenirken, yaşamsal tehlike ve kırığın hayat fonksiyonlarına etkisi ile ilgili belirleyici olması bakımından, kırığın yeri, ne tür bir kırık olduğu, kırığın sayısı önem taşımaktadır.
Anahtar Kelimeler: kafa kemik kırığı, adli rapor, trafik kazası, adli tıp

ORCID ID of the authors: ÜŞ. 0000-0002-3544-8871, BS. 0009-0008-8447-8349, TK. 0000-0003-3164-2316, NP. 0009-0004-9469-4898, ÖSK. 0000-0001-9312-6857, KK. 0000-0001-6009-0739

Received 08.09.2024 ***Accepted*** 07.10.2024 ***Online published*** 07.10. 2024

Correspondence: Ümit ŞİMŞEK- Eskişehir Osmangazi University, Faculty of Medicine, Department of Forensic Medicine, Eskisehir, Türkiye
e-mail: umitsimsek_26@hotmail.com

1. Introduction

Head trauma is an important cause of mortality and morbidity worldwide (1-5). Head traumas are more fatal than traumas involving other body parts (6). The rate of fatal injury due to head trauma has been reported to be 150-400 per 100.000 in the United States of America and the United Kingdom, and the rate of death due to head trauma has been reported to be 9-32 per 100.000 in the same countries (7). Fractures occur in the skull bones in 80% of fatal head traumas (1,7). In studies related with head traumas, it has been reported that the occurrence of skull bone fracture due to head trauma affects the morbidity, treatment modality and hospitalization time of the patient (8). In our country, there are not enough academic studies presenting data on the incidence and epidemiology of head trauma.

Head trauma and fractures in the skull bones may occur as a result of traffic accidents, effective actions such as fights and beatings, injuries caused by impact with a blunt object or falling from a height, and gunshot wounds (1-3,9,10). In a study conducted by Tsai et al. with 5,430 head trauma patients, it was reported that 52.4% of head bone fractures were caused by traffic accidents (11).

Due to their origin, skull bone fractures can be encountered in forensic medicine practice (10). In a study conducted in Eskişehir and including 306 cases in which all forensic bone fractures were evaluated, it was reported that 57.8% of the cases had skull fractures (12). Article 87 of the Turkish Penal Code (TPC) states that *"if intentional injury causes bone fracture or dislocation in the body, the penalty determined according to the above article is increased by up to half according to the effect of the fracture or dislocation on life functions"* (13,14). In practice, the effect of the fracture on life functions should be defined when preparing a forensic report on patients with skull fractures. In the guideline on the evaluation of injury crimes in terms of forensic medicine in the Turkish Penal Code, the grades of bone fractures and their life-threatening status are included in detail. It is defined as "life-threatening" when the inner and outer plates of the skull bones are fractured together (15). It has been reported that all forms of fractures involving only the outer tabula in regions of the skull with inner and outer tabula are not life-threatening and the effect on life functions is 1 (mild) degree. It was reported that each of the linear bone fracture lines in the skull (even if they cross more than one bone) has a grade 3 (moderate) impact on life functions. It is recorded that the effect of collapse fracture and pedestal fracture in the skull on life functions is 5 (severe) degrees (15). In the same guideline, it is recorded that a deficit of 5-25 cm2 in the skull bones should be considered as weakness of function, and losses of more than 25 cm2 should be considered as loss of function (15).

As in all forensic cases, hospital notes are very important when preparing the forensic report in cases with skull fractures. The relevant clinicians and radiologists must accurately describe the location, size, type and number of the skull fracture. If these data are not recorded regularly in the hospital file, the forensic report cannot be prepared correctly.

In the present study, we aimed to evaluate the demographic data, injury characteristics, clinical findings accompanying bone fracture, forensic reports of the cases admitted to our department and to share them with the literature.

2. Materials and Methods

In this study, the cases of non-fatal traumatic skull fractures that did not result in death who were admitted to our department between 01.01.2014 and 31.12.2023 were included in the study. Hospital documents, radiographs, CT scans, MR images and investigation documents of the cases were retrospectively analyzed. Age, gender, type of event, origin of the event, fractured bone, other accompanying findings and forensic report contents were analyzed. The data were uploaded to a package statistical program, chi-square and percentage analyses were performed and $p<0.05$ was accepted as significant.

The study was approved by the local ethics committee.

3. Results

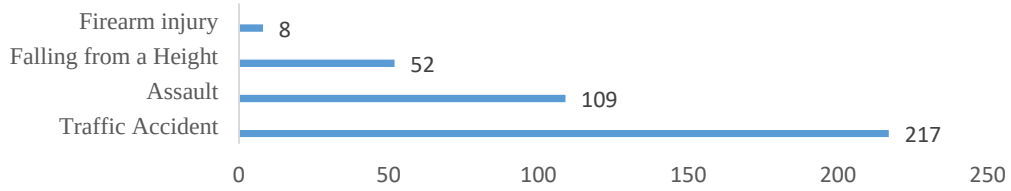
In the 10-year period covered by the study, 386 cases of non-fatal skull fractures were evaluated in our department.

It was determined that 294 (75.6%) of the cases were male and 92 (24.4%) were female, the youngest case was 2 years old and the oldest case was 78 years old, the mean age of the cases was 37±9.6 years and 78 cases (20.2%) were younger than 18 years. The distribution of pediatric and adult cases according to gender and origin of the incident is presented in Table 1. A significant relationship was found between gender and age group (P<0.001). While 24.1% of the male cases were younger than 18 years of age, only 7.6% of the female cases were younger than 18 years of age.

Table 1. Distribution of cases according to age group and gender

		Gender				T^2	p
		Male		Female			
		n	%	n	%		
Age Group	< 18	71	24,1	7	7,6	11,890	<0,001
	18 and over	223	75,9	85	92,4		
Total		294	100,0	92	100,0		

Of the cases, 269 (69.7%) were accidents and 117 (30.3%) were the result of effective actions such as fights, beatings and gunshot wounds. The most common cause of skull fractures was traffic accidents (n=217, 56.2%). 52 cases (13.5%) were injured as a result of accidental fall from a height, 109 cases (28.2%) were injured as a result of assault involving contact with a hard object or ground, and 8 cases (2.1%) were gunshot wounds (Graph 1). All of the firearm cases were assault with a firearm and no suicide attempt or accidental incident was encountered. A significant relationship was found between origin and gender (P<0.001). 29% of male and 15.2% of female patients were injured as a result of effective action.



Graph 1. Distribution of cases according to the way the events occurred

Table 2. Distribution of the origin of the cases according to gender

		Gender				T^2	p
		Male		Female			
		n	%	n	%		
Origin of the incident	Accident (Traffic accident=217, Fall from Height=52)	191	71,0	78	84,8	13,027	<0,001
	Effective action (Assault=109, Firearm injury=8)	103	29,0	14	15,2		

Total	294	100,0	92	100,0

The most common fracture was the frontal bone (n=206, 53.4%). In 112 cases (29.0%), the frontal bone was fractured in isolation, in 76 cases (19.7%) the frontal and parietal bones were fractured together, in 18 cases (4.7%) the temporal and frontal bones were fractured together, and in 27 cases (7.0%) the temporal and parietal bones were fractured together. In 94 cases (24.4%) parietal bone, in 45 cases (11.6%) temporal bone and in 14 cases (3.6%) occipital bone were fractured in isolation. The distribution of fractured skull bones according to event types is presented in Table 3. It was determined that there was no significant correlation between the fractured bones and event types (P>0.05).

Table 3. Distribution of broken bones according to event types

Fractured Bone	**Event Type**								**Total**
	Traffic Accident		**Falling**		**Assault**		**Firearm injury**		
	n	%	n	%	n	%	n	%	
Frontal	60	27,6	17	32,7	31	28,4	4	50,0	112
Parietal	51	23,5	13	25,0	28	25,7	2	25,0	94
Frontoparietal	51	23,5	7	13,5	18	16,5	0	0	76
Temporal	26	12,0	6	11,5	11	10,1	2	25,0	45
Temporoparietal	14	6,5	4	7,7	9	8,3	0	0	27
Frontotemporal	8	3,7	3	5,7	7	6,4	0	0	18
Oksipital	7	3,2	2	3,9	5	4,6	0	0	14
Total	217	100,0	52	100,0	109	100,0	8	100,0	386

I^2 = 38,276, P>0,05

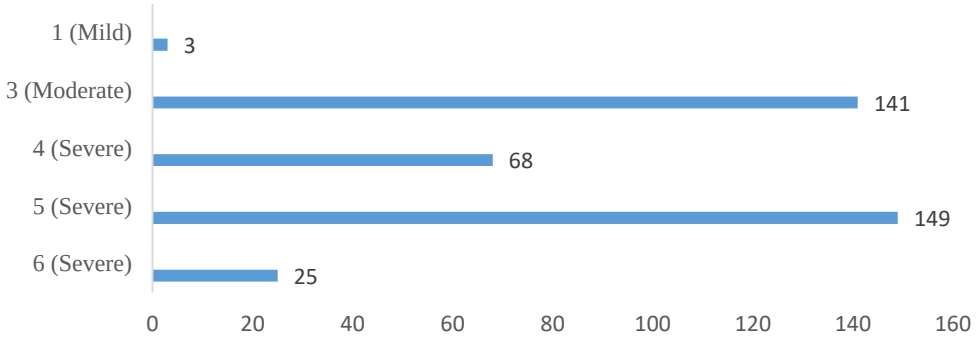
It was determined that 209 (54.1%) of the cases had linear fractures, 174 (45.1%) had comminuted and/or collapse fractures, and 3 (0.8%) had only external tabular fractures. The distribution of fractured skull bones according to fracture types is presented in Table 4. It was determined that there was no significant relationship between the fractured bone and fracture types (P>0.05). When it was evaluated whether the inner and outer tabula were fractured together in bones with tabula, it was determined that the outer tabula of the frontal bone was fractured isolated in only 3 cases (0.8%). It was reported that these 3 cases did not cause life-threatening injuries, but caused injuries that could not be treated with simple medical intervention. In all other cases (n=383, 99.3%), it was reported as life-threatening and could not be treated with simple medical intervention.

Table 4. Distribution of fractured bones according to fracture types

Fractured Bone	**Fracture Type**						**Total**
	Linear Fracture		**Fragmented / Collapse Fracture**		**Fracture of the outer tabula**		
	n	%	n	%	n	%	
Frontal	61	29,2	48	27,6	3	100,0	112
Parietal	44	21,1	50	28,7	0	0	94
Frontoparietal	43	20,6	33	19,0	0	0	76
Temporal	33	15,7	12	6,9	0	0	45
Temporoparietal	11	5,3	16	9,2	0	0	27
Frontotemporal	9	4,3	9	5,2	0	0	18
Occipital	8	3,8	6	3,4	0	0	14
Total	209	100,0	174	100,0	3	100,0	386

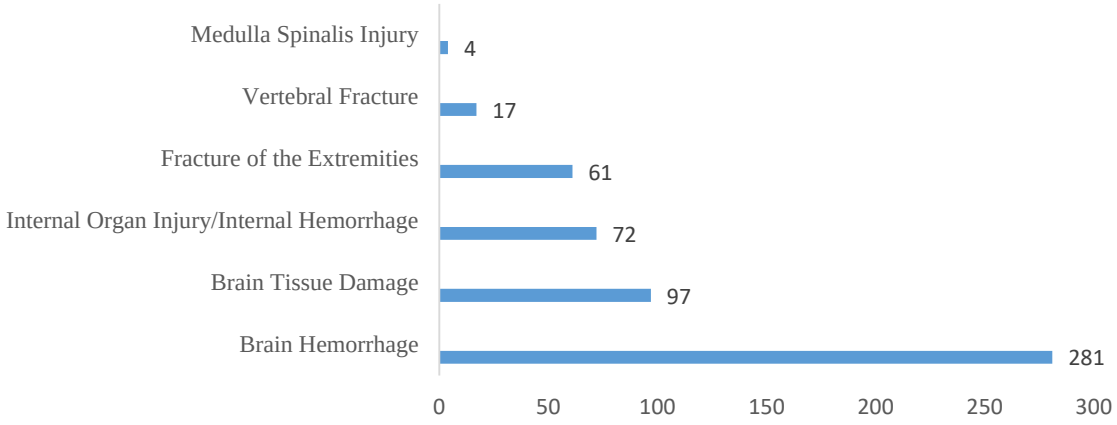
X2 = 20,850 P>0,05

The evaluation of skull bone fractures according to the grades of bone fractures in the guideline for forensic evaluation of injury crimes in the Turkish Penal Code is presented in graph 2. In 3 cases (0.8%) where only the outer tabula was fractured, the effect of the bone fracture on life functions was evaluated as 1 (Mild), in 141 cases (36.5%) as 3 (Moderate), in 68 cases (17.6%) as 4 (Severe), in 149 cases (38.6%) as 5 (Severe), in 25 cases (6.5%) as 6 (Severe). Only skull fractures were evaluated during grading. Other accompanying bone fractures were excluded except for skull fractures. 6 cases (1.6%) were reported to have impaired function due to a 5-25 cm2 defect after skull fracture. No patient with loss of function due to skull fracture was found.



Graph 2. Distribution of the effects of head bone fractures on life functions

In 105 cases (27.2%), the injury was an isolated skull fracture. In 281 cases (72.8%), cerebral hemorrhage accompanied the skull fracture. In 97 cases (25.1%), brain tissue was damaged in addition to cerebral hemorrhage. In 72 cases (18.7%) internal organ injury and internal bleeding, in 61 cases (15.8%) fractures of the extremities, in 17 cases (4.4%) vertebral fractures, and in 4 cases (1.0%) damage to the medulla spinalis were seen in addition to skull fractures (Graph 3). In 224 cases (58%), bone fractures were surgically intervened. In 162 cases (42%), non-surgical treatments were applied.



Graph 3. Findings Accompanying Head Bone Fracture

Of the cases, 269 (69.7%) were accidents and 117 (30.3%) were the result of effective actions such as fights, beatings and gunshot wounds. The most common cause of skull fractures was traffic accidents (n=217, 56.2%). 52 cases (13.5%) were injured as a

result of accidental fall from a height, 109 cases (28.2%) were injured as a result of assault involving contact with a hard object or ground, and 8 cases (2.1%) were gunshot wounds (Graph 1). All of the firearm cases were assault with a firearm and no suicide attempt or accidental incident was encountered. A significant relationship was found between origin and gender (P<0.001). 29% of male and 15.2% of female patients were injured as a result of effective action.

The most common fracture was the frontal bone (n=206, 53.4%). In 112 cases (29.0%), the frontal bone was fractured in isolation, in 76 cases (19.7%) the frontal and parietal bones were fractured together, in 18 cases (4.7%) the temporal and frontal bones were fractured together, and in 27 cases (7.0%) the temporal and parietal bones were fractured together. In 94 cases (24.4%) parietal bone, in 45 cases (11.6%) temporal bone and in 14 cases (3.6%) occipital bone were fractured in isolation. The distribution of fractured skull bones according to event types is presented in Table 3. It was determined that there was no significant correlation between the fractured bones and event types (P>0.05).

It was determined that 209 (54.1%) of the cases had linear fractures, 174 (45.1%) had comminuted and/or collapse fractures, and 3 (0.8%) had only external tabular fractures. The distribution of fractured skull bones according to fracture types is presented in Table 4. It was determined that there was no significant relationship between the fractured bone and fracture types (P>0.05). When it was evaluated whether the inner and outer tabula were fractured together in bones with tabula, it was determined that the outer tabula of the frontal bone was fractured isolated in only 3 cases (0.8%). It was reported that these 3 cases did not cause life-threatening injuries, but caused injuries that could not be treated with simple medical intervention. In all other cases (n=383, 99.3%), it was reported as life-threatening and could not be treated with simple medical intervention.

The evaluation of skull bone fractures according to the grades of bone fractures in the guideline for forensic evaluation of injury crimes in the Turkish Penal Code is presented in graph 2. In 3 cases (0.8%) where only the outer tabula was fractured, the effect of the bone fracture on life functions was evaluated as 1 (Mild), in 141 cases (36.5%) as 3 (Moderate), in 68 cases (17.6%) as 4 (Severe), in 149 cases (38.6%) as 5 (Severe), in 25 cases (6.5%) as 6 (Severe). Only skull fractures were evaluated during grading. Other accompanying bone fractures were excluded except for skull fractures. 6 cases (1.6%) were reported to have impaired function due to a 5-25 cm2 defect after skull fracture. No patient with loss of function due to skull fracture was found.

In 105 cases (27.2%), the injury was an isolated skull fracture. In 281 cases (72.8%), cerebral hemorrhage accompanied the skull fracture. In 97 cases (25.1%), brain tissue was damaged in addition to cerebral hemorrhage. In 72 cases (18.7%) internal organ injury and internal bleeding, in 61 cases (15.8%) fractures of the extremities, in 17 cases (4.4%) vertebral fractures, and in 4 cases (1.0%) damage to the medulla spinalis were seen in addition to skull fractures (Graph 3). In 224 cases (58%), bone fractures were surgically intervened. In 162 cases (42%), non-surgical treatments were applied.

4. Discussion

It is known that forensic injuries are mostly seen in males and in the young age group (16-19). Two different studies conducted in Çanakkale and Erzurum showed that boys were more frequently exposed to forensic injuries in childhood (20,21). In a study conducted in Sakarya in which 6,412 forensic cases were evaluated, it was reported that 72% of the cases were male and the mean age of the cases was 31.9 years (22). In a study conducted in Edirne, it was found that 78% of the forensic cases admitted to the emergency department were male and the mean age of the cases was 30.5 years (23). In a study by Adeleye et al. on head traumas, it was reported that males were exposed to head trauma three times more than females (24). Çırak et al. reported that 70% of the patients hospitalized in the Neurosurgery Clinic due to head trauma were male (25). In a study conducted in Taiwan, it was reported that 60% of patients with traumatic head bone fractures

were male (11). Akgül et al. reported that 75.5% of head trauma patients admitted to the emergency department were male and the mean age was 34 years (26). In the present study, in accordance with the literature, 294 (75.6%) of the cases were male and 92 (24.4%) were female and the mean age of the cases was 37±9.6 years. A significant relationship was found between gender and age group (P<0.001). While 24.1% of the male cases were under 18 years of age, only 7.6% of the female cases were under 18 years of age. It is thought that the reason for this is that boys are more involved in social life and are exposed to forensic injuries more than girls in our society.

In general, it is known that traffic accidents are the most common type of injury in forensic injuries involving all systems and body parts (6-18). It has also been reported that traffic accidents are one of the most common causes of head traumas (3,9,27-30). In a study conducted by Jha et al. in Nepal, it was reported that head trauma was the cause of death in 77 (62.1%) of 124 patients who died due to traffic accidents (31). In a study conducted in Ankara, it was found that the fatal injury was in the head region in 80.9% of the patients who died due to traffic accidents (32). In a study conducted in Eskişehir, it was reported that 72.4% of the patients who died due to traffic accidents had head trauma (33). In a study conducted by Işık et al. in Samsun, it was reported that 75% of the patients with head trauma evaluated in the Neurosurgery Clinic were admitted due to traffic accidents (9). In the present study, the most common cause of skull fractures was determined to be traffic accidents in accordance with the literature. In our study, 56.2% (n=217) of the patients had skull fractures as a result of traffic accidents. While 269 (69.7%) of the cases were accidents, 117 (30.3%) were the result of effective actions such as fights, beatings and gunshot wounds. 52 cases (13.5%) were injured as a result of a fall from a height, 109 cases (28.2%) were injured as a result of a beating involving contact with a hard object or floor, and 8 cases (2.1%) had gunshot wounds. A significant relationship was found between origin and gender (P<0.001). 29 % of the male and 15.2 % of the female cases were injured as a result of effective action. Injuries of males as a result of fight and effective action were found to be compatible with the forensic literature (13,14,16-18).

Assault has an important place in injuries related to forensic traumatology (16-19,34). In a study by Keleş et al. it was reported that 64% of 1280 patients who presented to the emergency department due to assault had head trauma (35). Injury may occur with many different mechanisms during assault. Fatal injuries may occur by hitting with a hard object or hitting a hard surface (34,36). Fractures in the skull bones, cerebral hemorrhage and brain tissue destruction may occur by hitting the head with a hard object or hitting the head with a hard object with kinetic energy (37). In the present study, 109 cases (28.2%) were found to have been injured as a result of beating involving contact with a hard object or the ground. In our study, a significant correlation was found between origin and gender (P<0.001). 29% of the male and 15.2% of the female patients were injured as a result of effective action. In a study in Kırıkkale in which emergency department admissions due to head trauma were evaluated, it was reported that 11% of male and 3.2% of female patients with head trauma presented due to assault (26). As in other forensic cases, assault injuries are more common in males.

One of the common causes of head trauma and skull fractures is falls (25,26,38). Factors such as the height of the fall, age of the person and body structure determine the damage to occur due to the fall (3). In a study conducted in Kahramanmaraş in which cases of death due to falling from a tree were evaluated, it was found that 76% of the cases had signs of head trauma and 57.1% had fractures in the skull bones (39). In a meta-analysis study conducted by Ongel et al. on falls, it was reported that the head region was injured most frequently (45.1%) due to falls (40). In a study conducted in Van, 44% of the patients admitted to the Neurosurgery Clinic because of head trauma were injured due to falls (25). In a study conducted in Minnesota in which head bone fractures were evaluated, it was reported that 36% of the cases were injured

due to falls (41). In the present study, it was found that 52 cases (13.5%) were injured as a result of falling from a height, fractures occurred in the skull bones and the origin of all fall cases was accidental.

Gunshot wounds to the head are usually fatal (42,43). In a study in which 21 cases of firearm injuries affecting the head region were evaluated, it was reported that 5 of the cases died, 5 remained bedridden and 11 recovered (44). In a study conducted in Erzurum in which gunshot wounds resulting in death were evaluated, it was reported that the most common injury occurred in the head region (45). In a study conducted in Şanlıurfa, it was reported that the fatal injury was in the head region in 48.2% of the patients who died due to firearm injuries (46). Bullets cause skull fracture, brain destruction and cerebral hemorrhage together (47). Since these injuries usually result in death, only 8 cases (2.1%) were found to have gunshot wounds in the present study. In the present study, fatal cases could not be included. These 8 cases had skull fractures due to gunshot wounds and recovered afterwards.

In the forensic report, it should be written in detail whether the injury causes life-threatening danger, whether it can be eliminated by simple medical intervention, the degree of bone fracture and its effect on life functions, whether it causes weakness or loss of function (48). These matters are important in terms of constituting the basis for the penalty to be imposed on the person who caused the injury. All these issues are included in the guideline for the evaluation of injury crimes in terms of forensic medicine in the Turkish Penal Code (15). In the present study, isolated fracture of the outer tabula of the frontal bone was found in 3 cases (0.8%). It was reported that these 3 cases were not life-threatening and caused injuries that could not be treated with simple medical intervention. In all other cases (n=383, 99.3%), it was reported that the injury was life-threatening and could not be treated with simple medical intervention. In 3 cases (0.8%) the effect of bone fracture on life functions was evaluated as 1 (Mild), in 141 cases (36.5%) as 3 (Moderate), in 68 cases (17.6%) as 4 (Severe), in 149 cases (38.6%) as 5 (Severe), in 25 cases (6.5%) as 6 (Severe). 6 cases (1.6%) were reported to have impaired function due to a 5-25 cm2 defect after skull fracture. No patient with loss of function due to skull fracture was found.

In studies on skull bone fractures, it has been reported that linear fractures are the most common fracture type in skull bone fractures because they require lower kinetic energy (3,41,49). In a study conducted in Minnesota in which 1097 cases with skull fracture were evaluated, it was reported that 585 (53%) of the cases had linear fractures (41). In a study conducted by Şimşek et al. with 152 patients with skull bone fractures, it was reported that 99 (65.1%) of the cases had linear fractures (3). In the present study, 54.1% (n=209) of the cases had linear fractures in accordance with the literature. There was no significant correlation between fractured bone and fracture types (P>0.05).

It was determined that the frontal bone was fractured most frequently (n=206, 53.4%). In 112 cases (29.0%), the frontal bone was fractured in isolation, in 76 cases (19.7%) the frontal and parietal bones were fractured together, and in 18 cases (4.7%) the temporal and frontal bones were fractured together. In a study by Şimşek et al. on head traumas, it was reported that the frontal bone was fractured most frequently (3). In a study by Dumitru et al. on frontal bone fractures, it was emphasized that frontal bones were more frequently affected by high-energy traumas such as traffic accidents (37). In the present study, 53.6% (60/112) of isolated frontal bone fractures occurred due to traffic accidents.

In our study, it was determined that skull bone fractures occurred most frequently in males, in the young adult age group, most frequently due to traffic accidents and in the form of linear fractures in the frontal bone. The findings were consistent with the literature. When preparing a forensic report on skull fractures, the location of the fracture, the type of fracture and the number of fractures are important in terms of determining the risk to life and the effect of the fracture on life functions. It is important for the relevant clinicians and radiologists to keep detailed

hospital notes in terms of forensic investigation. In forensic cases, it is important to perform a detailed examination, to perform the necessary examinations and to write an understandable forensic report in accordance with the guidelines as a result of the findings obtained, in terms of the rapid and correct functioning of the justice system. In life-threatening forensic cases such as skull fractures, the rapid and accurate preparation of forensic reports is an important part of a fair trial, which is the most fundamental right of individuals.

REFERENCES

1. Pakiş I, Sav AM. The importance of pathological findings after head trauma in forensic medicine I. Türkiye Ekopatoloji Dergisi, 2004;10(1-2), 27-30.
2. Egemen E, Börcek AÖ. Approach to Head Trauma. Journal of Intensive Care Medicine, 2013;11(1), 1-12.
3. 3.Şimşek M, Kaya M, Hiçdönmez T, Süslü TH, Gergin YE. Research of Epidemyological and Prognostic Factors on Cranial Fractures Depends Trauma.Türk Nöroşirürji Dergisi. 2013;23(1): 12-7.
4. Levi L, Guilburg JN, Linn S, Feinsod M: The association between skull fracture, intacranial pathology and outcome in pediatric head injury. Br J Neurosug 5:617-625,1991.
5. Şimşek O, Hiçdönmez T, Hamamcıoğlu MK, Kılınçer C, Parsak T, Tiryaki M, Kurt I, Çobanoğlu S. Pediatric head injuries: a retrospective analysis of 280 patients. Turkish Journal of Trauma & Emergency Surgery 11:310-317, 2005
6. Baiden F, Anto-Ocrah M, Adjei G, Gyaase S, Abebrese J, Punguyire D, Moresky RT. Head injury prevalence in a population of injured patients seeking care in Ghana, West Africa. Frontiers in neurology, 2022;13, 917294.
7. Davis RL, Robertson DM. Cerebrospinal trauma. Chapter 19. In: Textbook of Neuropathology. Third ed Baltimore, Maryland: Williams & Wilkins, 1997; 1179-1232.
8. Lemole M, Behbahani M. Retrospective Study of Skull Base Fracture: A Study of Incidents, Complications, Management, and Outcome Overview from Trauma-One-Level Institute over 5 Years. Journal of Neurological Surgery Part B: Skull Base, 2013;74(S 01), A239.
9. Işık HS, Bostancı U, Yıldız Ö, Özdemir C, Gökyar A: Retrospective analysis of 954 adult patients with head injury: an epidemiological study. Turkish Journal of Trauma & Emergency Surgery 2011;17:46-50.
10. Adeleye AO, Ogun MI. (2017). Clinical epidemiology of head injury from road-traffic trauma in a developing country in the current era. Frontiers in neurology, 2017;8, 695.
11. Tsai YC, Rau CS, Huang JF, Chang YM, Chia KJ, Hsieh TM, Hsieh, C. H. The association between skull bone fractures and the mortality outcomes of patients with traumatic brain injury. Emergency Medicine International, 2022;(1): 1296590.
12. Karbeyaz K, Gündüz T, Balcı Y. Forensic medicine approach to bone fractures in the framework of the new Turkish penal code. Turkish Journal of Trauma & Emergency Surgery 2010;16 (5):453-458.
13. 13.Çelik C, Ata U. About Medicolegal Evaluation of the Effects of Bone Fracture/Dislocation on Life Functions. The Bulletin of Legal Medicine, 2022;27(1):93-101
14. Çeliksöz AH, Emiral E, Doğan B, Şimşek Ü, Karbeyaz K. Evaluation of bone fractures in forensic qualified cases. Journal of Forensıc Medicine, 2020;34(3):134-140
15. 15.Türk Ceza Kanunu'nda Tanımlanan Yaralama Suçlarının Adli Tıp Açısından Değerlendirilmesi Rehberi https://www.atk.gov.tr/tckyaralama 24-06-19.pdf Erişim 30.07.2024
16. Bilgin NG, Dokgöz H, Kar H. Comparison of Judicial Reports Prepared According to the Old and New Turkish Penal Code. The Bulletin of Legal Medicine, 2006;11:64-70.
17. Altun G, Azmak D, Yılmaz A, Yılmaz G. Characteristics of forensic cases applied to the Emergency Department of Trakya University Faculty of Medicine. The Bulletin of Legal Medicine, 1997;2:62-6.
18. Koylu S. Karbeyaz, K. The Evaluation of the Relationship Between Alcohol and Forensic Cases Admitted to Eskişehir Osmangazi University Faculty of Medicine Department of

Forensic Medicine. Osmangazi Journal of Medicine , 2018;41, 216-225.
19. Seviner M, Kozacı N, Ay M, Açıkalın Akpınar A, Çökük A, Gülen M, Acehan S, Karanlık Genç M, Satar S. Analysis of Judicial Cases at Emergency Department. Cukurova Medical Journal, 2013:38;250 - 260.
20. Yıldırım A. Trauma Profile and Characteristics of Intentional Injuries in Pediatric Forensic Cases Who Admitted to Emergency Service: A Retrospective Analysis. Klinik Tıp Pediatri Dergisi, 2016;8(3), 34-39.
21. Kılınç BB, Kök AN, Şener MT. Causes and Consequences of Childhood Physical Traumas: Retrospective Analysis of Forensic Cases. Turkiye Klinikleri Journal of Pediatrics, 2023;32(2):75-82.
22. Küçük E, Günel C. Demographic Characteristics of Forensic Investigation in Emergency Service 2016;Sakarya Medical Journal, 6(2):100-5
23. Altun G, Azmak AD, Yılmaz A, Yılmaz G. The characteristics of the cases which admitted to Emergency Department of Trakya University Medical Faculty. Bulletin of Forensic Medicine, 1997;2(2), 62-66.
24. Adeleye AO, Ogun MI. Clinical epidemiology of head injury from road-traffic trauma in a developing country in the current era. Frontiers in neurology, 2017;8, 695.
25. Çırak B, Berker M, Özcan OE, Özgen T. An Epidemiological Study of Head Trauma: Results of Treatment. Turkish Journal of Trauma & Emergency Surgery 1999; 5(2): 90-92
26. Akgül M, Burulday V. Evaluation Results of the Cases Applied to the Emergency Unit with Cause of Head Trauma. The Journal of Kırıkkale University Faculty of Medicine 2016; 18(3), 134-138.
27. Carson HJ. Brain trauma in head injuries presenting with and without concurrent skull fractures. Journal of Forensic and Legal medicine 2009;16:115-120.
28. Yagmur F, Celik S, Yener Z, Koral F, Yaman T, Sezer Y, Kandemir E. Head Trauma–Related Deaths Among Preschool Children in Istanbul, Turkey. The American Journal of Forensic Medicine and Pathology, 2016;37(1), 35-39.
29. Lee KS. Estimation of the incidence of head injury in Korea: an approximation based on national traffic accident statistics. Journal of Korean medical science, 2001;16(3), 342-346.
30. Bekman MZ. Head Traumas. Turkiye Klinikleri Journal of Internal Medical Sciences, 2007;3(5), 35-43.
31. Jha S, Yadav BN, Karn A, Aggrawal A, Gautam, A. P. Epidemiological study of fatal head injury in road traffic accident cases: a study from BPKIHS, Dharan. Health renaissance, 2010;8(2), 97-101.
32. Değirmenci B, Akar T, Demirel B. Evaluation of Mortal Traffic Accidents in Terms of Forensic Medicine Gazi Medical Journal, 2015;26(4):143-47.
33. Karbeyaz K, Balcı Y, Çolak E, Gündüz T. Characteristics of Traffic Accidents in Eskişehir Between 2002 and 2007. Turkiye Klinikleri Journal of Forensic Medicine and Forensic Sciences, 2009;6(2), 65-73.
34. Svider PF, Johnson AP, Folbe AJ, Carron MA, Eloy JA, Zuliani G. Assault by battery: battery-related injury in the head and neck. The Laryngoscope, 2014;124(10), 2257-2261.
35. Keleş A, Alkaş GB, Kadı G, Aslaner MA, Bildik F, Kılıçaslan İ, Demircan A. The Characteristics of Assaulted Victims Presented to A University Emergency Department: Can Head Trauma İn Male Patients Be Considered A Clue For Assaults? Turkish Journal of Trauma & Emergency Surgery, 2022;28(12):1690-5.
36. Fornari MJ, Badolato GM, Rao K, Goyal MK, McCarter R, Donnelly KA. Violent injury as a predictor of subsequent assault-related emergency department visits among adolescents. Journal of Adolescent Health, 2023;72(6), 972-976.
37. Dumitru M, Vrinceanu D, Banica B, Cergan R, Taciuc IA, Manole F, Popa-Cherecheanu M. Management of aesthetic and functional deficits in frontal bone trauma. Medicina, 2022;58(12): 1756.
38. Çökük A, Kozacı N, Ay MO, Açıkalın A, Seviner M, Satar S. Evaluation of Head Trauma Cases in the Emergency Department. Cukurova Medical Journal, 2013;38(1), 63-71.
39. Avşar A, Okdemir E, Keten A, Karanfil R. Tree falling related death. Dicle Medical Journal, 2015,42(3), 331-334.
40. Ongel K, Katırcı E, Uludağ H, Mergen H, Uzun E, Kişioğlu AN. Examination of the cases of falling from height according to the publications Tıp Araştırmaları Dergisi: 2008;6 (3) :175 -180.
41. Nelson EL, Melton LJ 3rd, Annegers JF, Laws ER, Offord KP: Incidence of

skull fractures in Olmsted Country, Minnesota. Neurosurgery 15:318-324, 1984
42. Doctor VS, Farwell DG. Gunshot wounds to the head and neck. Current opinion in otolaryngology & head and neck surgery, 2007;15(4), 213-218.
43. Menezes JM, Batra K, Zhitny VP. A Nationwide analysis of gunshot wounds of the head and neck: morbidity, mortality, and cost. Journal of Craniofacial Surgery, 2023,34(6), 1655-1660.
44. Çırak B, Güven M B, Kıymaz N, Işık S. Cranial Gunshot Injuries and Treatment Approaches. Turkish Journal of Trauma & Emergency Surgery, 2000; 6(4): 241-243.
45. Kır MZ, Ketenci HÇ, Başbulut AZ, Özsoy S. Evaluation of Deaths Due to Gunshot Injuries in Erzurum. Journal of Forensic Medicine.2012;26(1):27-37.
46. Dündar AS, Altın İ. Cases Under the Age of 18 who Are Determined to Have Died due to Firearm Injury at Şanlıurfa Forensic Medicine Branch Directorate Examination. Phoenix Medical Journal, 2023;5(3), 206-210.
47. Yaman O, Dağlı AT, Güvercin AR, Kuzeyli K. Gunshot Wound to Head. Journal of Nervous System Surgery, 2014;4(2), 69-73.
48. Karbeyaz K, Gündüz T, Akkaya H, Urazel B, Kökçüoğlu MA. Watch out for judicial reports; Eskisehir experience. Sted/Sürekli Tıp Eğitimi Dergisi, 2012;21(5), 292-296.
49. Yoganandan N, Pintar FA. Biomechanics of temporo-parietal skull fracture. Clinical Biomechanics, 2004;19(3), 225-239.

Ethics

Ethics Committee Approval: The study was approved by Eskisehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 53, Date: 02.05.2024).
Informed Consent: This study did not require informed consent.
Authorship Contributions:
Copyright Transfer Form: Copyright Transfer Form was signed by all authors.
Peer-review: Internally peer-reviewed.
Conflict of Interest Disclosure: There is no conflict of interest among the authors.
Sources of Funding: There is no funding/sponsorship for this study.

Osmangazi Journal of Med, 2025;47(1):146-150
DOI: 10.20515/otd. 1516838

Case Report
Olgu Sunumu

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Angiosarcoma of the Breast: Case Report

Memenin Anjiyosarkomu: Olgu Sunumu

[1]Bartu Badak, [1]Arda Şakir Yılmaz, [1]Mithat Mert Yurdakul, [2]Nazlı Sena Şeker, [2]Furkan Albayrak

[1]Department of General Surgery, Eskisehir Osmangazi University, Faculty of Medicine, Eskisehir, Türkiye
[2]Department of Pathology, Eskisehir Osmangazi University, Faculty of Medicine, Eskisehir, Türkiye

BB. 0000-0003-3465-8719
ASY. 0000-0003-1269-0814
MMY. 0009-0002-8816-8256
NSŞ. 0000-0003-4588-7250
FA. 0009-0002-6283-1507

Correspondence / Sorumlu yazar:
Arda Şakir YILMAZ

Department of General Surgery, Eskisehir Osmangazi University, Faculty of Medicine, Eskisehir, Türkiye

e-mail: dr.ardayilmaz@hotmail.com

Abstract: Angiosarcoma is a rare and aggressive tumor of the breast arising from endothelial cells. It is usually associated with chronic lymphedema or radiation therapy. The diagnosis is made by biopsy and there is no specific finding on mammography. In this study, we report a 59-year-old woman with a history of radiotherapy for invasive ductal carcinoma who subsequently developed primary angiosarcoma of the breast. Angiosarcoma of the breast was first documented in 1887 and is classified as primary and secondary. While surgical R0 resection is recommended for the treatment of these tumors with unclear etiology, the significance of axillary lymph node dissection remains uncertain. Adjuvant radiotherapy has been shown to reduce the local recurrence rate, but adjuvant chemotherapy and radiotherapy have no significant effect on 5-year survival. Although there is no consensus on treatment regimens, it is concluded that more comprehensive studies should be conducted in a larger sample.
Keywords: Breast, angiosarcoma, radiotherapy

Özet: Anjiyosarkom, memede nadir görülen ve endotel hücrelerinden kaynaklanan agresif bir tümördür. Genellikle kronik lenfödem veya radyasyon tedavisi ile ilişkilidir. Tanı biyopsi ile konur ve mamografide spesifik bir bulgusu yoktur. Bu çalışmada, invaziv duktal karsinom nedenli radyoterapi öyküsü olan ve sonrasında primer meme anjiyosarkomu gelişen 59 yaşındaki kadın hasta sunulmaktadır. Memenin anjiyosarkomu, ilk olarak 1887 yılında belgelenmiş olup, primer ve sekonder olarak sınıflandırılır. Etiyolojisi tam olarak açıklanamamış olan bu tümörlerin tedavisi için cerrahi R0 rezeksiyon önerilirken, aksiller lenf nodu diseksiyonunun önemi belirsizdir. Adjuvan radyoterapinin lokal rekürrens oranını azalttığı, ancak adjuvan kemoterapi ve radyoterapinin 5 yıllık sağ kalım üzerinde belirgin bir etkisi olmadığı görülmüştür. Tedavi rejimleri konusunda fikir birliği olmamakla birlikte, daha geniş örneklemde daha kapsamlı çalışmalar yapılması gerektiği sonucuna varılmıştır.
Anahtar Kelimeler: Meme, anjiyosarkom, radyoterapi

Informed Consent: The authors declared that informed consent form was signed by the patient.

Copyright Transfer Form: Copyright Transfer Form was signed by the authors.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Applications: AŞY, BB, MMY. Concept: BB. Design: MMY. Data Collection or Processing: MMY. Analysis or Interpretation: AŞY, MMY, FA, NSŞ. Literature Review: AŞY, NSŞ. Writing: AŞY.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support

Received 16.07.2024
Accepted : 12.11.2024
Published :13.11.2024

How to cite/ Atıf için: Badak B, Yilmaz AS, Yurdakul MM, Seker NS, Albayrak F, Angiosarcoma of the Breast: Case Report , Osmangazi Journal of Medicine,2025;47(1): 146-150

1. Introduction

Angiosarcoma is an aggressive tumor originating from endothelial cells. Although most commonly found in the breast, it is a rare mesenchymal tumor that can also occur in the heart, pericardium, liver, skin, bone, and soft tissues. Breast angiosarcoma constitutes approximately 0.04% of all malignant breast tumors (1). Its etiology can be spontaneous or associated with factors such as chronic lymphedema or radiation therapy. However, these types of angiosarcomas account for about 50% of all breast sarcomas and are linked to radiation therapy used in the treatment of primary invasive breast cancer (2, 3). The latency period for radiation-induced breast sarcoma development can range from 3 to 20 years. The incidence has been reported to be 0.3% at ten year and 0.5% at fifteen year (4). Angiosarcoma does not have specific findings on mammography, and diagnosis is generally confirmed through biopsy (5).

This case presentation discusses a 59-year-old female patient with primary breast angiosarcoma, supported by current literature.

2. Case Report

A 59-year-old female patient presented to our clinic with a raised lesion approximately 2 cm in diameter adjacent to the areola on her right breast. She has a medical history significant for diabetes mellitus, hypertension, and hypothyroidism. Her past medical records revealed a history of left modified radical mastectomy in 2010 due to carcinoma in situ of the left breast, which was diagnosed as high-grade comedo-type carcinoma in situ with microinvasive foci on final pathology, prompting clinical follow-up. During her second year of follow-up, a 1 cm lesion was detected in the right breast, confirmed as invasive ductal carcinoma on stereotactic excisional biopsy. Subsequently, she underwent segmental mastectomy and axillary dissection of the right breast, with no residual tumor found on pathology. She received chemotherapy and radiotherapy to the right breast as part of her oncological treatment. In her sixth year of follow-up, she presented with the 2 cm raised lesion near the areola of the right breast, which was biopsied and pathologically diagnosed as an atypical vascular tumor. After obtaining informed consent, she underwent right mastectomy (Figure 1). Histopathological evaluation of the specimen revealed tumor cells diffusely positive for CD31 (Figure 2). Additionally, at 200x magnification, numerous irregular and anastomosing vascular structures containing atypical endothelial cells were observed (Figure 3). Based on these findings, she was diagnosed with breast angiosarcoma and referred to medical oncology for continuation of oncological management.

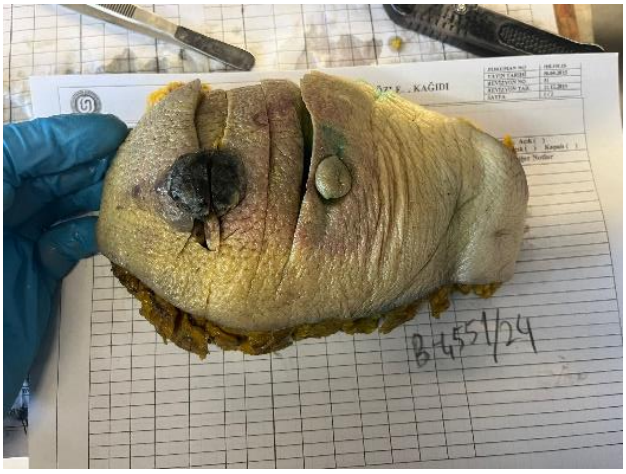


Figure 1. Right breast mastectomy material

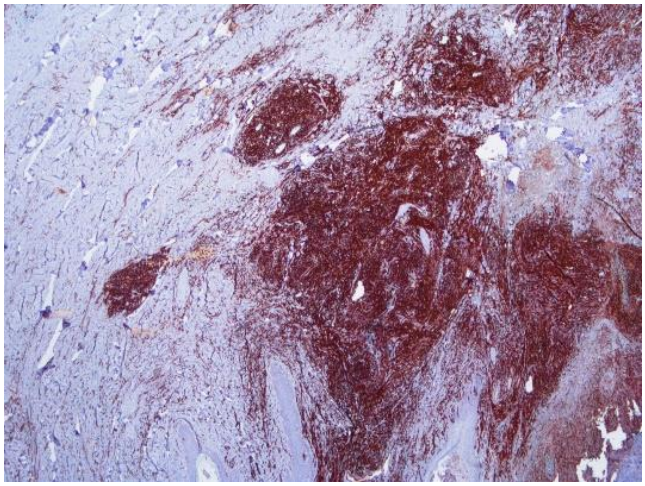


Figure 2. Tumor cells showing diffusely strong positivity for CD31

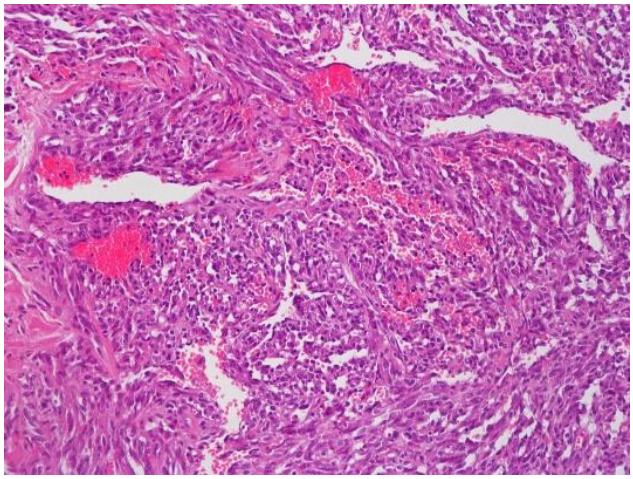


Figure 3. Tumorous lesion consisting of numerous irregular and anastomosing vascular structures containing atypical endothelial cells at 200 magnification

3. Discussion

Breast angiosarcoma was first documented by Schmit in 1887 (6). These malignant tumors originate from the endothelium of vascular structures surrounding the lobules of the breast. They are classified into primary and secondary types etiologically. Primary breast angiosarcoma tends to have an aggressive course with a generally poor prognosis, more commonly affecting women aged 30-50 years without any significant medical history or risk factors (7). The etiology of secondary breast angiosarcoma remains unclear; however, chronic lymphedema, exposure to chemical agents, ionizing radiation, chronic inflammation, and trauma are proposed etiological factors (8). Additionally, 6-12% of breast angiosarcomas occur in women during pregnancy and lactation, suggesting a potential role of high estrogen levels in etiology (9).

In a retrospective study by Kim et al. (10) involving 15 patients, 73.3% presented with masses larger than 5 cm, and the 5-year survival rate was 28.3% for tumors larger than 5 cm compared to 66.7% for tumors 5 cm or smaller, though statistically significant difference was not demonstrated (p=0.096).

There is no standardized treatment regimen for breast angiosarcoma, but surgical R0 resection is generally recommended as the cornerstone of treatment for all angiosarcomas (10). Toesca et al. (11) showed in their study

that total mastectomy is not superior to breast-conserving surgery, emphasizing the primary goal of surgery is to achieve negative surgical margins. In our case, a total mastectomy was performed considering the previous history of segmental mastectomy and the loss of nipple during negative surgical margins.

The role of axillary lymph node dissection in breast angiosarcoma is uncertain because angiosarcoma primarily metastasizes hematogenously (12). Merino et al. (13) in their study of 13 patients diagnosed with breast angiosarcoma, did not find axillary lymph node involvement. Therefore, in the absence of palpable axillary lymph nodes preoperatively, axillary lymph node dissection is not recommended (13). Axillary dissection was not performed because the patient had a history of axillary dissection and no positive axillary lymph nodes.

Although there is no consensus on adjuvant and neoadjuvant treatment protocol, studies have shown that adjuvant radiotherapy reduces local recurrence rates (14). Another study indicated a positive impact of adjuvant radiotherapy on recurrence-free survival when evaluating both primary and secondary angiosarcomas together. Concerns about angiosarcomas developing secondary to radiation exposure and complications related to radiation exist; however, this study suggests that patients who receive postoperative radiotherapy have lower rates of local recurrence (15). Conversely, Kim et al. (10) stated in their study that adjuvant chemotherapy and radiotherapy did not significantly affect 5-year survival ($p>0.05$).

In our patient with a history of radiotherapy after right segmental mastectomy and axillary dissection, radiation oncology did not recommend radiotherapy due to T1N0 and surgical margin negative angiosarcoma in the pathology after mastectomy, but adjuvant chemotherapy (Taxol) was started by medical oncology. Her treatment is still ongoing.

In conclusion, there is no consensus on the treatment of breast angiosarcomas, but R0 surgical resection is the recommended initial approach. Further comprehensive studies with larger sample sizes are needed to reach consensus on chemotherapy and radiotherapy regimens.

REFERENCES

1. Varghese B, Deshpande P, Dixit S, Koppiker CB, Jalnapurkar N. Primary Angiosarcoma Of the Breast: A Case Report. J Radiol Case Rep. 2019;13(2):15-25.
2. Vorburger SA, Xing Y, Hunt KK, Lakin GE, Benjamin RS, Feig BW, et al. Angiosarcoma of the breast. Cancer. 2005;104(12):2682-8.
3. Bonito FJP, de Almeida Cerejeira D, Dahlstedt-Ferreira C, Oliveira Coelho H, Rosas R. Radiation-induced angiosarcoma of the breast: A review. Breast J. 2020;26(3):458-63.
4. Meijer S, Peretz T, Gaynor JJ, Tan C, Hajdu SI, Brennan MF. Primary colorectal sarcoma. A retrospective review and prognostic factor study of 50 consecutive patients. Arch Surg. 1990;125(9):1163-8.
5. Arora TK, Terracina KP, Soong J, Idowu MO, Takabe K. Primary and secondary angiosarcoma of the breast. Gland Surg. 2014;3(1):28-34.
6. Stout AP. Hemangio-Endothelioma: A Tumor Of Blood Vessels Featuring Vascular Endothelial Cells. Ann Surg. 1943;118(3):445-64.
7. Scow JS, Reynolds CA, Degnim AC, Petersen IA, Jakub JW, Boughey JC. Primary and secondary angiosarcoma of the breast: the Mayo Clinic experience. J Surg Oncol. 2010;101(5):401-7.
8. Esposito E, Avino F, di Giacomo R, Donzelli I, Marone U, Melucci MT, et al. Angiosarcoma of the breast, the unknown-a review of the current literature. Transl Cancer Res. 2019;8(Suppl 5):S510-s7.
9. Georgiannos SN, Sheaff M. Angiosarcoma of the breast: a 30 year perspective with an optimistic outlook. Br J Plast Surg. 2003;56(2):129-34.
10. Kim YJ, Ryu JM, Lee SK, Chae BJ, Kim SW, Nam SJ, et al. Primary Angiosarcoma of the Breast: A Single-Center Retrospective Study in Korea. Curr Oncol. 2022;29(5):3272-81.
11. Toesca A, Spitaleri G, De Pas T, Botteri E, Gentilini O, Bottiglieri L, et al. Sarcoma of the breast: outcome and reconstructive options. Clin Breast Cancer. 2012;12(6):438-44.
12. Ragavan S, Lim HJ, Tan JW, Hendrikson J, Chan JY, Farid M, et al. Axillary Lymph Node Dissection in Angiosarcomas of the Breast: An

Asian Institutional Perspective. Sarcoma. 2020;2020:4890803.
13. Merino MJ, Carter D, Berman M. Angiosarcoma of the breast. Am J Surg Pathol. 1983;7(1):53-60.
14. Hodgson NC, Bowen-Wells C, Moffat F, Franceschi D, Avisar E. Angiosarcomas of the breast: a review of 70 cases. Am J Clin Oncol. 2007;30(6):570-3.
15. Abdou Y, Elkhanany A, Attwood K, Ji W, Takabe K, Opyrchal M. Primary and secondary breast angiosarcoma: single center report and a meta-analysis. Breast Cancer Res Treat. 2019;178(3):523-33.

Osmangazi Journal of Med, 2025;47(1): 151-157
DOI: 10.20515/otd. 1594823

Case Report
Olgu Sunumu

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

A Turkish Patient with Spastic Paraplegia Type 4 with a De Novo Missense Mutation in the SPAST Gene

SPAST Geninde De Novo Missense Mutasyonu Olan Spastik Parapleji Tip 4'lü Bir Türk Hasta

Emine İkbal Atlı, Hakan Gürkan, Engin Atlı

Trakya University, Faculty of Medicine, Department of Medical Genetics, Edirne, Türkiye

EİA. 0000-0001-9003-1449
HG. 0000-0002-8967-6124
EA. 0000-0002-3937-5243

Correspondence / Sorumlu yazar:
Emine İkbal ATLI

Trakya University, Faculty of Medicine,
Department of Medical Genetics, Edirne

e-mail: emine.ikbal@gmail.com

Abstract: Spastic paraplegia type 4 is a common type of autosomal-dominant pure hereditary spastic paraplegia that is brought on by variations in the SPAST gene. In this investigation, the SPAST genotype and clinical phenotype of a Turkish SPG4 patient were analyzed in an effort to provide additional genetic evidence for the pathophysiology of HSP. The clinical data of the proband and his family members were collected. After complete genomic DNA was isolated from peripheral blood, whole-exome sequencing technology was used to identify genes and analyze the pathogenicity of variants. Variants suspected of being pathogenic were found. Within this family, Sanger sequencing was used for verification. The sequencing of SPAST revealed a de novo missense c.1496G > A (p.Arg499His) and missense MEFV c.2177T>C (p.Val726Ala) variants. The parents and paternal relatives did not have the SPAST mutation. De novo variants of the c.1496G > A mutation in SPAST can arise at notably high frequencies. We discussed the case of a Turkish patient and examined the clinical characteristics of patients with the p.Arg499His variation in SPAST that have been documented in the literature. There is growing evidence that the p.Arg499His missense mutation in SPAST may be linked to early-onset HSP. The majority of pathogenic mutations were found in the protein's AAA domain, according to analysis of SPAST sequences; this may be closely related to the pathophysiology of SPG4. The results of this investigation may broaden the range of therapeutic applications for the p.Arg499His mutation in SPAST and offer a chance to investigate the genotype-phenotype relationship of SPG4 in more detail.
Keywords: Spastic Paraplegia Type 4, SPAST Gene, Missense Mutation

Informed Consent: Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images. Ethical approval was not required for this study in accordance with local/ national guidelines.

Copyright Transfer Form: Copyright Transfer Form was signed by the authors.

Peer-review: Internally peer-reviewed.

Authorship Contributions:

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author, [EIA].

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support

Acknowledgments: The authors would like to thank the family for their participation in this project.

Özet: Otozomal dominant kalıtsal spastik paraplejilerin yaygın bir formu, SPAST genindeki mutasyonlardan kaynaklanan spastik parapleji tip 4'tür. Bu araştırmada, HSP'nin patofizyolojisi için ek genetik kanıt sağlamak amacıyla bir Türk SPG4 hastasının SPAST genotipi ve klinik fenotipi analiz edildi. Vaka Sunumu: Probandın ve aile üyelerinin klinik verileri toplandı. Periferik kandan tüm genomik DNA izole edildikten sonra, genleri tanımlamak ve mutasyonların patojenitesini analiz etmek için tüm ekzom dizileme teknolojisi kullanıldı. Şüpheli patojenik mutasyonlar belirlendi. Bu aile için doğrulama Sanger dizilemesi ile gerçekleştirildi. SPAST gen dizilemesi sonucu de novo missense c.1496G > A (p.R499H) ve missense MEFV c.2177T>C (p.Val726Ala) mutasyonları belirlendi. SPAST mutasyonu ebeveynlerde ve akrabalarda yoktu. c.1496G > A mutasyonu SPAST'ta belirgin derecede yüksek oranlarda de novo varyant olarak ortaya çıktığı bilinmektedir. SPAST'ta p.Arg499His mutasyonu olan literatürde bildirilen hastaların klinik özelliklerini inceledik. Elde edilen kanıtlar, erken başlangıçlı HSP ile SPAST'taki p.Arg499His anlamsız mutasyonu arasında olası bir ilişki olduğunu göstermektedir. SPAST dizi analizi, patojenik mutasyonların çoğunun proteinin AAA kodunda meydana geldiğini ve bunun SPG4 patogenezi ile yakın bir ilişkide olabileceğini ortaya koymuştur. Bu araştırmanın sonuçları, SPAST'taki p.Arg499His mutasyonu için terapötik uygulama yelpazesini genişletebilir ve SPG4'ün genotip-fenotip ilişkisini daha ayrıntılı olarak araştırma şansı sunabilir.
Anahtar Kelimeler: Spastik Parapleji Tip 4, SPAST Geni, Missense Mutasyon

Received 02.12.2024
Accepted : 27.12.2024
Published : 30.12.2024

How to cite/ Atıf için: Atlı Eİ, Gürkan H, Atlı E, A Turkish Patient with Spastic Paraplegia Type 4 with a De Novo Missense Mutation in the SPAST Gene, Osmangazi Journal of Medicine,2025;47(1): 151-157

1. Introduction

The progressively developing weakness and spastic paraplegia of the lower limbs are the hallmarks of hereditary spastic paraplegia (HSP), a heterogeneous group of genetic neurodegenerative disorders. There is significant genetic and clinical variety in HSP. It is estimated that 0.1 to 9.6/100,000 people have HSP [1,2]. Autosomal dominant (AD), autosomal recessive (AR), X-linked recessive (XR), or mitochondrial inheritance are the possible modes of inheritance. Spastic paraplegia 4 (SPG4) resulting from variants in the spastin (SPAST) gene contributes for 40–45% of HSP cases in AD-HSP, with SPG3A (ATL1) and SPG31 (REEP1) accounting for roughly 10% and 6.5% of HSP cases, respectively [3,4]. The most severe pathological alteration in HSP is the bilateral corticospinal pathways in the spinal cord experiencing axonal degeneration and/or demyelination. The thoracic segment exhibits the most severe abnormalities in this regard. The clinical manifestations of HSP are varied and complex, with a high risk of missing and incorrect diagnoses. The pathogenesis of HSP is not entirely understood. When diagnosing HSP and identifying phenotypic subgroups, genetic testing is a crucial supplementary tool [5].

More than 60 genes and 80 distinct gene loci have been linked to HSP to date. The most frequently mutated gene in SPG4 among them is SPAST, which is found at 2p22.3 and has 17 exons that span over 90 kb. The 616 amino acid protein known as spastin is a member of the ATPase family, which controls the quantity, length, and vibrancy of microtubules in the cell. Thus far, 683 pathogenic variants in the SPAST gene have been documented. The most prevalent types of variants are nonsense and missense variants, which make up about 37% of instances. The two primary forms of pathogenesis are the increase of function of pathogenic spastin isoforms and the loss of spastin cleavage function [6-8].

Here, we describe a female patient whose de novo SPAST gene variation results in a clinically SPG4 phenotype.

2. Case Report

A 3-year-old girl was the youngest of three siblings born to healthy and unrelated parents. Our patient has walking and speaking delay and global developmental delay. Her 11-year old sister and 13-year-old brother were unaffected. She was born by cesarean section after an healthy pregnancy. Our patient was born in the 39th week of pregnancy with a weight of 3045 g. The patient started to stand at the 10th month, but independent walking was not observed. The anterior fontanelles closed at the 12th month. The nape hairline is low and the forehead is prominent. At 28 months, the family noticed that she was unable to crawl on her hands and knees or stand without assistance. She could not walk independently until now. Our patient also has speech delay. The patient uses single words. she did not have any cerebellar, sensory, or autonomic dysfunctions and was mentally normal. Furthermore, routine laboratory tests were normal. The motor symptoms of the patient progressed slowly, and her gait became increasingly slow and spastic over time.

As a result of the patient's clinical evaluation, karyotyping, Array comparative genomic hybridisation (a-CGH) and Whole-exome sequencing (WES) analysasseses were performed. aCGH analysis and karyotyping were performed first, followed by WES (provided aCGH profile and karyotyping had been normal). Following phytohemagglutinin-stimulated short-term lymphocyte culture, our patient's heparinized peripheral blood sample was used for chromosome analysis utilizing the Giemsa trypsin banding method.

In accordance with the manufacturer's instructions, genomic DNA was extracted from venous blood using a kit (Qiagen, Germany). The human genome CGH Agilent 180K custom array was used for the aCGH study. Every genomic coordinate is in build GRCh37/hg19.

The SPAST genotype and clinical phenotype of an SPG4 family were examined in an effort to find additional genetic evidence for the pathophysiology of HSP. The clinical data of the proband and his family members were collected. The genomic DNA of the patient and his parents was extracted from peripheral blood after obtaining written informed consent, whole-exome sequencing technology was used to identify genes and determine the pathogenicity of variants. Variants suspected of being pathogenic were found. Within this family, Sanger sequencing was used for verification.

Whole-exome sequencing

The Illumina NextSeq550 (Illumina Inc., San Diego, CA, USA) system was used to analyze a clinical

exome gene panel that contained 6699 OMIM genes. Libraries were set up in accordance with the manufacturer's guidelines. Utilizing the Qubit dsDNA BR Assay kit (Invitrogen, Carlsbad, CA), the generated libraries were subjected to quality control. The Illumina NextSeq550 (Illumina Inc., San Diego, CA, ABD) system was used to generate Fastq files. The QIAseq Targeted DNA Panel procedure (Qiagen, Hilden, Germany) was followed in the preparation of libraries encompassing the target genes. Libraries were sequenced using the Illumina NextSeq550 (Illumina Inc., San Diego, CA, USA) system after the target enrichment procedure. Variant Call Format file ordering and quality control were done using QCI analysis (Qiagen, Hilden, Germany). Using Ingenuity software (Qiagen, Hilden, Germany), a variance analysis was conducted.

As a result of WES analysis, the missense NM_014946.4(SPAST):c.1496G>A (p.Arg499His) variant in our patient was identified in the dbSNP database with the number rs878854991. As a result of WES analysis (Figure 1), the patient also had missense NM_000243.3(MEFV):c.2177T>C (p.Val726Ala) was detected. NM_000243.3(MEFV):c.2177T>C (p.Val726Ala) variant was inherited from the father of the patient.

Bioinformatic analysis

The UCSC hg19 human reference genome construct was then used to align the reads. The variants were annotated using ANNOVAR (http://annovar.openbioinformatics.org/en/latest/). Excluded were common locations with population allele rates greater than 5% as reported by the 1000 Genome Project, dbSNP 13 and ExAC databases. The 2015 ACMG Standards and Guidelines were used to interpret the pathogenicity of the variations. This variant was deemed pathogenic based on the following evidence of pathogenicity, as per the norms and guidelines of the American College of Medical Genetics and Genomics: Supporting: PP2, PP3, PP5, moderate: PM1, PM2, PM5, and strong: PS2. A thorough search of ClinVar, the Human Gene Mutation Database (HGMD), and published literature was done to confirm variants The pathogenicity of the new variants found in this study was predicted using Polyphen-2, SIFT, and Mutation Taster.

Sanger sequencing

Using primer-designed software, primers were created to target the location between the upstream and downstream regions of the exon in order to identify the potentially pathogenic mutation. Sanger sequencing was then carried out to confirm the mutation in the proband and other family members. A cosegregation study was performed using the characteristics of this family to evaluate potential pathogenic mutation locations. We validated the p.Arg499His mutation in exon 13 of the SPAST gene, which was in a heterozygous state, using Sanger sequencing.

On the other hand, the patient's parents and younger sister did not have the mutation. The patient in this family carried a mutation that neither her parents nor her healthy sibling had. Her oldest sister and brother were also healthy. These observations suggest that the mutation occurred de novo in the patient.

Table 1. Clinical findings of hereditary spastic paraplegia

Patient	Nucleotide change	Amino acid change	Sex	Duration age	Age of onset	Walking achievement	Functional impairment	Spasticity	Increased reflexes	Dysarthria	MRI or intelligence	Literature
1	c.1496G>A	p.Arg499His	M	12 y	14m	No	6	3	Exaggerated muscle stretch reflexes of both the upper and lower limbs	9 y, lost ability to speak at 12 y	More pronounced hyperintense bilateral PLICs in FLAIR sequences	Ogasawara et al., (2019) (9)
2	c.1496G>A	p.Arg499His	F	36 y	<2 y	NA	6	3	NA	<6 y	Mild hyperintensities in corticospinal tracts (white arrows) in	de Souza et al.,(2016) (10)

											T2-weighted and FLAIR sequences	
3	c.1496G>A	p.Arg499His	F	13 y	20m	No	5	LL spasticity	Lower limb hyper-reflexia	<11 y	Intellectual disability	Gillespie et al.,(2018) (11)
4	c.1496G>A	p.Arg499His	F	5 y	1 y	22 m, hold on to furniture	4	NA	Yes	Early expressive language delays	Low-lying conus medullaris with minimal thickening of the filum terminale	Gillespie et al.,(2018) (11)
5	c.1496G>A	p.Arg499His	M	11 y	1.5 y	48 m, walk alone	2	NA		No	NA	Polymeris et al.,(2016) (12)
6	c.1496G>A	p.Arg499His	M	3 y	1 y	NA	NA	Spasticity	Lower extremity hyper-reflexia, Babinski sign	No	NA	Park et al.,(2015) (13)
7	c.1495C>T	p.Arg499Cys	M	20 y	13 y	NA		1	LL increased; UL normal/yes	No	NA	Depienne et al.,(2006) (14)
8	c.1496G>A	p.Arg499His	M	>40 y	Childhood	Limited walking without aid	3	3	Not determined	NA	NA	Depienne et al.,(2006) (14)
9	c.1495C>T	p.Arg499Cys	F	60 y	Childhood	NA	3	3	Lower limb increased; upper limb normal	NA	NA	Depienne et al.,(2006) (14)
10	c.1495C>T	p.Arg499Cys	NA	63 y	Childhood	Need help for daily life	6	3	LL, UL/bilateral	NA	NA	Ribaï et al.,(2008) (15)
11	c.1495C>T	p.Arg499Cys	NA	55 y	51 y	Need help for daily life	6	1	LL, UL/bilateral	NA	NA	Ribaï et al.,(2008)
12	c.1495C>T	p.Arg499Cys	NA	53 y	Adolescence	Partially need help for daily life	2	3	LL, UL/bilateral	NA	Cortical and subcortial atrophy, nonspecific WMH	Ribaï et al.,(2008) (15)
13	c.1495C>T	p.Arg499Cys	NA	47 y	4 y	Need help for daily life	5	3	LL, UL/bilateral	NA	Cortical atrophy	Ribaï et al.,(2008) (15)
14	c.1495C>T	p.Arg499Cys	NA	45 y	5 y	None	6	3	LL, UL/bilateral	NA	NA	Ribaï et al.,(2008) (15)
15	c.1495C>T	p.Arg499Cys	NA	43 y	Birth	Need help for daily life	5	3	LL/bilateral	NA	Cortical and subcortical atrophy	Ribaï et al.,(2008) (15)
16	c.1495C>T	p.Arg499Cys	NA	39 y	Childhood	Partially need help for daily life	6	3	LL, UL/bilateral	NA	NA	Ribaï et al.,(2008) (15)
17	c.1495C>T	p.Arg499Cys	NA	29 y	Birth	Partially need help for daily life	6	3	LL, UL/bilateral	NA	Normal	Ribaï et al.,(2008) (15)
18	c.1495C>T	p.Arg499Cys	NA	27 y	1 y	Partially need help for daily life	3	2	LL/bilateral	NA	NA	Ribaï et al.,(2008) (15)
19	c.1495C>T	p.Arg49	NA	24 y	Childhoo	Need	3	2	LL/bil	NA	NA	Ribaï et

		9Cys			d	help for daily life			ateral			al.,(2008) (15)
20	c.1496G>A	p.Arg499His	F	27 y	Childhood	No	6	Yes	Lower limb increased, positive Babinski sign	Speech is slow, slurred, and the voice diminishes at 22 y	thoracic spinal cord atrophy	Ribaï et al.,(2008) (15)
21	c.1496G>A	p.Arg499His	F	3 y	28 m	Need help for daily life	NA	NA	NA	Early expressive language delays	NA	this report

LL, lower limb; UL, upper limb. Functional impairment: 0—none, 1—no functional impairment but signs at examination, 2—mild, 3—moderate, 4—walking with one cane, 5—walking with two canes, and 6—wheelchair-bounded. Gait spasticity: 0—none, 1—mild, 2—moderate, and 3—severe.

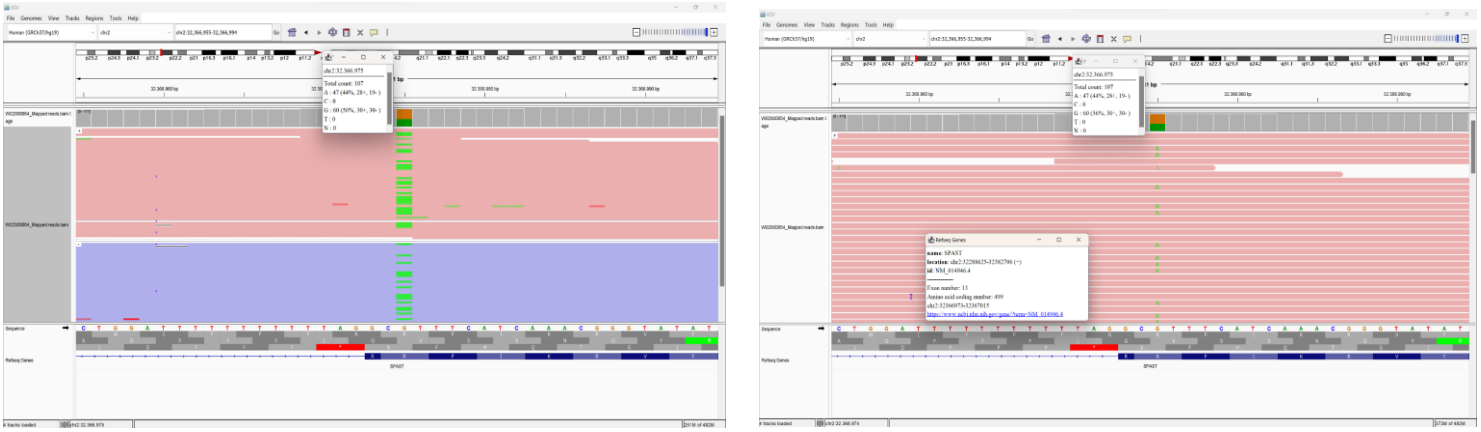


Figure 1. NM_014946.4(SPAST):c.1496G>A IGV image

3. Discussion

We detailed the clinical development of an SPG4 patient who carried a SPAST missense mutation. Numerous earlier studies have identified the p.Arg499His mutation in the SPAST gene as a disease-causing mutation [9]. This mutation is essential for microtubule-severing activity and is found in the spastin AAA ATPase cassette, which runs from amino acids 342 to 616. In patients with SPG4, more than 200 distinct variants at locations within the AAA region have been found [10]. Table 1 demonstrates that there were 20 patients with walking difficulties and lower limb spasticity who had p.Arg499His or p.Arg499Cys, an incidental variant for HSP [9,10-15]. With the exception of p.Arg499His (4/6), it starts early and affects certain people with dysarthria and mental deficiencies. In the present study, the patient also had walking and speech difficulties.

For SPAST mutations, the genotype-phenotype association has not yet been well defined. However, a growing body of evidence indicates that severe infantile-onset complex HSP is linked to the p.Arg499His mutation in SPAST [16].

Currently, HSP is thought to comprise a wide range of genetically diverse diseases[17]. Out of all HSP-SPAST cases, around 75% are hereditary, with de novo variants accounting for the other 25% of occurrences [5]. Patients with SPG4 are mostly treated for symptoms, as there is currently no cure. For impacted families, genetic counseling is crucial. HSP could also be considered and genetic testing should be done when people without a family history experience growing walking difficulties, lower limb spasticity, and other symptoms such tendon hyperreflexia.

The clinical traits and sequencing analysis findings of a patient with SPG4 were presented in the current study. The range of pathogenic variants causing SPG4 is increased by the discovery of a novel SPAST mutation, which also offers data for genetic counseling.

The current study's outcomes highlight the necessity of using molecular analysis to better identify certain variations and assess their functional significance in patients with spastic paraplegia.

In conclusion, we encountered a case of childhood-onset pure SPG4 phenotype caused by a de novo mutation in the SPAST gene in a Turkish patient. This work may increase our understanding of the variation spectrum of SPG4 and offer a clinical foundation for future investigations. This work may offer a chance to investigate the genotype-phenotype link of SPG4 in more detail and may help physicians who are doing genetic testing on patients who have difficult HSP with an early onset.

Established Facts and Novel Insights

Established Facts

· More than 60 genes and more than 80 distinct gene loci have been linked to hereditary spastic paraplegia (HSP) to date.

· The pathogenesis of HSP is not entirely understood.

· Spastic paraplegia 4 (SPG4) resulting from variants in the spastin (*SPAST*) gene contributes to 40–45% of HSP cases in AD-HSP, with SPG3A (ATL1) and SPG31 (REEP1) accounting for roughly 10% and 6.5% of HSP cases, respectively

Novel Insights

· Numerous earlier studies have identified the p.R499H mutation in the *SPAST* gene as a disease-causing mutation

· In patients with SPG4, more than 200 distinct variants at locations within the AAA region have been found

· Out of all HSP-*SPAST* cases, around 75% are hereditary, with *de novo* variants accounting for the other 25% of occurrences.

· The current study's outcomes highlight the necessity of using molecular analysis to better identify certain variations and assess their functional significance in patients with spastic paraplegia.

· In a Turkish patient, we found a case of pure SPG4 phenotype with childhood onset brought on by a de novo variation in the *SPAST* gene. This work may increase our understanding of the variation spectrum of SPG4 and offer a clinical foundation for future investigations.

REFERENCES

1. Varghese B, Deshpande P, Dixit S, Koppiker CB, Jalnapurkar N. Primary Angiosarcoma Of the Breast: A Case Report. J Radiol Case Rep. 2019;13(2):15-25.
2. Vorburger SA, Xing Y, Hunt KK, Lakin GE, Benjamin RS, Feig BW, et al. Angiosarcoma of the breast. Cancer. 2005;104(12):2682-8.
3. Bonito FJP, de Almeida Cerejeira D, Dahlstedt-Ferreira C, Oliveira Coelho H, Rosas R. Radiation-induced angiosarcoma of the breast: A review. Breast J. 2020;26(3):458-63.
4. Meijer S, Peretz T, Gaynor JJ, Tan C, Hajdu SI, Brennan MF. Primary colorectal sarcoma. A retrospective review and prognostic factor study of 50 consecutive patients. Arch Surg. 1990;125(9):1163-8.
5. Arora TK, Terracina KP, Soong J, Idowu MO, Takabe K. Primary and secondary angiosarcoma of the breast. Gland Surg. 2014;3(1):28-34.
6. Stout AP. Hemangio-Endothelioma: A Tumor Of Blood Vessels Featuring Vascular Endothelial Cells. Ann Surg. 1943;118(3):445-64.
7. Scow JS, Reynolds CA, Degnim AC, Petersen IA, Jakub JW, Boughey JC. Primary and secondary angiosarcoma of the breast: the Mayo Clinic experience. J Surg Oncol. 2010;101(5):401-7.
8. Esposito E, Avino F, di Giacomo R, Donzelli I, Marone U, Melucci MT, et al. Angiosarcoma of the breast, the unknown-a review of the current literature. Transl Cancer Res. 2019;8(Suppl 5):S510-s7.
9. Georgiannos SN, Sheaff M. Angiosarcoma of the breast: a 30 year perspective with an optimistic outlook. Br J Plast Surg. 2003;56(2):129-34.
10. Kim YJ, Ryu JM, Lee SK, Chae BJ, Kim SW, Nam SJ, et al. Primary Angiosarcoma of the Breast: A Single-Center Retrospective Study in Korea. Curr Oncol. 2022;29(5):3272-81.
11. Toesca A, Spitaleri G, De Pas T, Botteri E, Gentilini O, Bottiglieri L, et al. Sarcoma of the breast: outcome and reconstructive options. Clin Breast Cancer. 2012;12(6):438-44.
12. Ragavan S, Lim HJ, Tan JW, Hendrikson J, Chan JY, Farid M, et al. Axillary Lymph Node Dissection in Angiosarcomas of the Breast: An Asian Institutional Perspective. Sarcoma. 2020;2020:4890803.

13. Merino MJ, Carter D, Berman M. Angiosarcoma of the breast. Am J Surg Pathol. 1983;7(1):53-60.
14. Hodgson NC, Bowen-Wells C, Moffat F, Franceschi D, Avisar E. Angiosarcomas of the breast: a review of 70 cases. Am J Clin Oncol. 2007;30(6):570-3.
15. Abdou Y, Elkhanany A, Attwood K, Ji W, Takabe K, Opyrchal M. Primary and secondary breast angiosarcoma: single center report and a meta-analysis. Breast Cancer Res Treat. 2019;178(3):523-33.

Osmangazi Journal of Med, 2025;47(1): 158-162
DOI: 10.20515/otd. 1498147

Case Report
Olgu Sunumu

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Renal Cell Carcinoma with Thyroid and Bilateral Adrenal Gland Metastases

Tiroid ve Bilateral Adrenal Gland Metastazı olan Renal Hücreli Karsinom

[1]Bartu Badak, [1]İbrahim Kısalar, [1]Arda Şakir Yılmaz, [2]Emel Yaldır

[1]Department of General Surgery, Eskisehir Osmangazi University, Faculty of Medicine, Eskisehir, Türkiye
[2]Department of Pathology, Eskisehir Osmangazi University, Faculty of Medicine, Eskisehir, Türkiye

BB. 0000-0003-3465-8719
İK. 0009-0002-2316-0093
ASY. 0000-0003-1269-0814
EY. 0000-0001-7297-9869

Correspondence / Sorumlu yazar:
Arda Şakir YILMAZ

Department of General Surgery, Eskisehir Osmangazi University, Faculty of Medicine, Eskisehir, Türkiye

e-mail: dr.ardayilmaz@hotmail.com

Abstract: Renal cell carcinoma is the most common type of malignant kidney disease, representing more than 90% of cases. It frequently metastasizes to the lungs, bones, liver and brain. Thyroid and adrenal metastases are rare. In this case report, we present a 64-year-old man with renal cell carcinoma who developed bilateral adrenal metastases three years after right radical nephrectomy and thyroid metastases five years later. Renal cell carcinoma has a high metastasis rate and requires careful follow-up. The increasing use of non-invasive imaging modalities has increased the detection rates of rare adrenal and thyroid metastases. Due to the rarity of such cases, standard treatment protocols are not well defined, emphasizing the need for careful follow-up even years after surgery..
Keywords: Renal cell carcinoma, thyroid, adrenal, metastasis

Özet: Renal hücreli karsinom, vakaların %90'ından fazlasını temsil eden en yaygın malign böbrek hastalığı türüdür. Sıklıkla akciğerlere, kemiklere, karaciğere ve beyne metastaz yapar. Tiroid ve adrenal metastazlar nadirdir. Bu vaka raporunda, sağ radikal nefrektomiden üç yıl sonra iki taraflı adrenal metastaz ve beş yıl sonra tiroid metastazı gelişen renal hücreli karsinomlu 64 yaşındaki bir erkek hasta sunduk. Renal hücreli karsinomun yüksek metastaz oranı vardır ve dikkatli takip gerektirir. Non-invaziv görüntüleme yöntemlerinin artan kullanımı ile nadir görülen adrenal ve tiroid metastazlarının da tespit oranlarını artırmıştır. Bu tür vakaların nadir olması nedeniyle standart tedavi protokolleri iyi tanımlanmamıştır; bu da ameliyattan yıllar sonra bile dikkatli bir izlemenin gerekliliğini vurgulamaktadır.
Anahtar Kelimeler: Renal hücreli karsinom, tiroid, adrenal, metastaz

Informed Consent: The authors declared that informed consent form was signed by the patient.

Copyright Transfer Form: Copyright Transfer Form was signed by the authors.

Peer-review: Internally peer-reviewed.

Authorship Contributions: AŞY, BB, İK. Concept: BB. Design: İK. Data Collection or Processing: İK. Analysis or Interpretation: AŞY, AMŞ, ET. Literature Review: ASY, ET. Writing: ASY.**Conflict of Interest:** No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support

Received 08.06.2024
Accepted : 12.11.2024
Published :13.11.2024

How to cite/ Atıf için: Badak B, Yilmaz AS, Yaldir E, Renal Cell Carcinoma with Thyroid and Bilateral Adrenal Gland Metastases, Osmangazi Journal of Medicine,2025;47(1):158-162

1. Introduction

Renal cell carcinoma (RCC) is the most common form of malignant kidney disease, accounting for over 90% of all malignant kidney cases. RCC ranks as the sixth most frequent cancer type in men and the tenth in women (1). Men are generally more affected, with a male-to-female ratio of 1.5:1. The incidence rate is highest among patients aged 60 to 70 years (2). RCC has several histological variants, with clear cell RCC (75%), papillary RCC (10-15%), and chromophobe RCC (5%) being the most prevalent forms, collectively representing 90% of RCC cases (3). The bones, liver, and lungs are the most common sites of metastasis in RCC, with thyroid metastases typically emerging around ten years after initial diagnosis (4). In recent years, RCC diagnoses have increased due to incidental discoveries during diagnostic investigations conducted for other purposes (2). Ipsilateral adrenal metastasis occurs in 7-23% of RCC cases, whereas bilateral adrenal metastasis is quite rare (5). The thyroid gland and the head and neck region are also uncommon sites for metastasis (4).

In our case, we aim to present a patient who developed bilateral adrenal metastasis three years after right radical nephrectomy and thyroid metastasis observed in the fifth year, in light of the literature.

2. Case Report

A 64-year-old male patient, under follow-up for known RCC, presented to our clinic due to thyroid nodules detected during his 5-year follow-up. The patient had undergone a right radical nephrectomy for RCC five years earlier and subsequently received treatment with the tyrosine kinase inhibitor sunitinib. During the patient's 3-year follow-up, a computed tomography (CT) scan revealed suspicious areas in both adrenal glands. A subsequent dynamic adrenal CT scan showed hypervascular lesions in the axial sections, with precontrast high densities and 70% absolute washout values, indicative of metastases. These lesions measured 4 cm in the right adrenal gland and 4.2 cm in the left adrenal gland. Percutaneous biopsy of these newly developed lesions confirmed RCC metastasis. The patient continued oncological treatment, and at the 5-year follow-up, a control thoracic CT scan revealed hypodense, nodular lesions with calcified foci in both thyroid glands (Figure 1). Consequently, the patient was referred to our clinic.

Upon reevaluation, we requested a thyroid ultrasound. The ultrasound revealed a cystic nodular lesion measuring 11x9x15 mm in the right thyroid lobe and a hypoechoic lesion with calcified foci measuring 9x10x15 mm in the left lobe. Fine-needle aspiration biopsy from the left thyroid lobe showed atypical epithelial cells with clear cytoplasm, nuclear enlargement, and prominent nucleoli forming papilla-like structures in Papanicolaou-Giemsa-stained cytocentrifuge smears and cytoblock sections (Figure 2). Immunohistochemistry revealed positivity for PAX2 and CD10, weak focal positivity for RCC, and negativity for thyroid transcription factor-1 (TTF-1) and thyroglobulin (Figures 3-5). Based on these cytopathological findings and the patient's history, the diagnosis was determined to be RCC metastasis. The patient was subsequently evaluated by the oncology council and referred to the medical oncology clinic for further oncological follow-up.

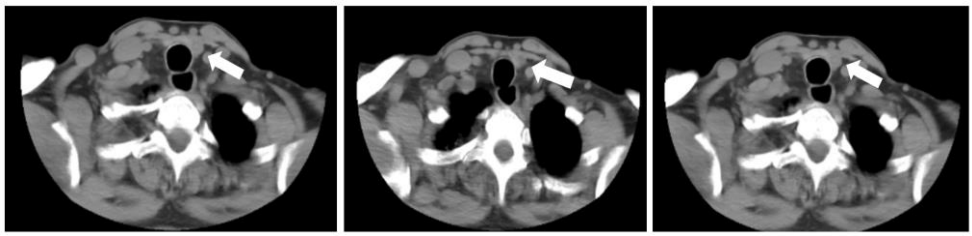


Figure 1. A nodule thought to be metastatic was observed in the left thyroid lobe.

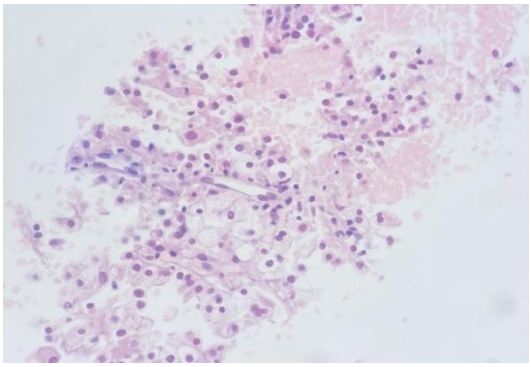


Figure 2. Tumoral cells with clear cytoplasm and pleomorphic nuclei in the cell block, along with features consistent with tumor necrosis, H&E stain.

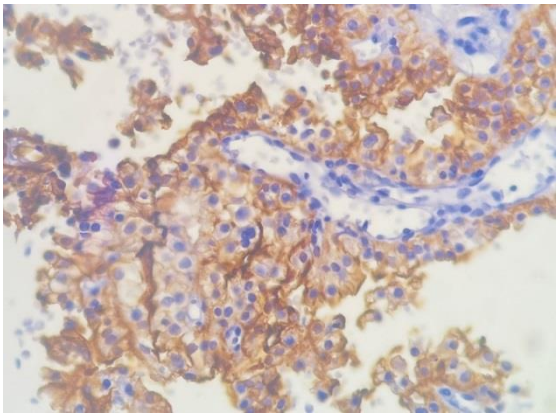


Figure 3. CD10 positivity, immunohistochemical staining.

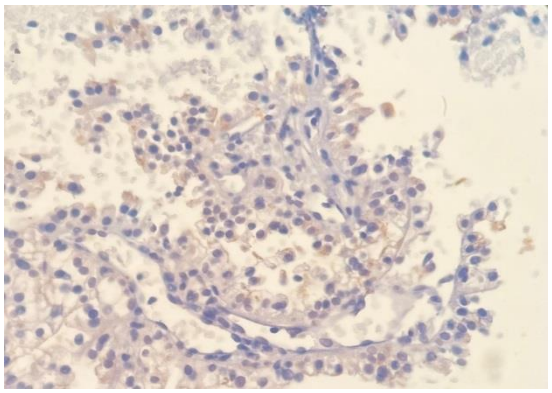


Figure 4. Weak focal positivity for RCC, immunohistochemical staining.

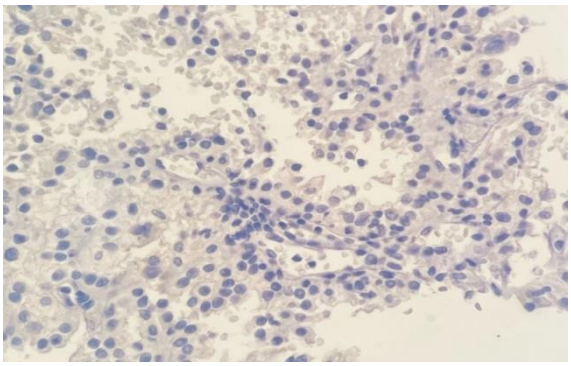


Figure 5. TTF-1 negativity, immunohistochemical staining.

3. Discussion

Approximately 25-30% of patients diagnosed with RCC present with metastatic disease at the time of diagnosis. Furthermore, 20-40% of patients with initially localized disease may develop metastases after surgical treatment. Therefore, the frequency of metastasis in RCC is quite high, necessitating close monitoring of these patients. RCC most commonly metastasizes to the lungs, but bones, liver, and brain are also frequent sites of metastasis. Less commonly, metastases can occur in the adrenal glands, lymph nodes, and other organs.

Thyroid metastasis from RCC is rare and often presents as a rapidly growing, painless cervical mass during follow-up after nephrectomy. Similar to primary thyroid tumors, thyroid metastasis can manifest with symptoms such as hoarseness, dysphagia, dyspnea, neck pain, cough, and epistaxis. The diagnostic algorithm for thyroid metastasis from RCC is not significantly different from that for primary thyroid tumors. Fine-needle aspiration biopsy can establish the diagnosis (6). Markers used to identify primary thyroid malignancies, such as TTF-1 and calcitonin, are negative, whereas immunohistochemical markers such as cytokeratin, vimentin, and CD-10 are positive for metastatic renal cell tumors (7).

Despite the rarity of thyroid metastasis from RCC, RCC is the most common malignancy metastasizing to the thyroid, accounting for 48.1% of such cases (8-9). Other common malignancies metastasizing to the thyroid include colorectal cancer (10.4%), lung cancer (8.3%), breast cancer (7.8%), and sarcomas (4.0%) (10).

The likelihood of adrenal metastasis from RCC is relatively low. Among patients undergoing nephrectomy, the incidence of isolated ipsilateral and contralateral adrenal metastasis is 3-5% and 0.7%, respectively. The literature reports the rate of bilateral adrenal metastasis to be less than 0.5% (11-12).

The widespread use of non-invasive radiological imaging methods, such as ultrasonography and CT, has led to an increase in the diagnosis of such lesions. In our case, the diagnosis was made during routine CT follow-up in the absence of any symptoms and was confirmed by ultrasound and histopathological examination.

Surgery for thyroid metastases is intended as palliative therapy and local control of metastatic disease and should be part of a broader systematic and multidisciplinary approach (13). Whether there is a difference between total and subtotal thyroidectomy is a controversial issue. Many studies suggest that there is no difference in survival between the two operations. Beutner et al. found that 5-year survival was better with total thyroidectomy than with non-total thyroidectomy, but the results were not statistically significant (P=0.49) and suggested that there was no improvement in survival when compared with total thyroidectomy and partial thyroidectomy (14). Another retrospective study from Europe showed that 5-year overall survival with thyroid metastasectomy was 51% (15).

The decision regarding the choice of treatment for metastatic renal cell carcinoma depends on different factors, including the extent of disease, sites of metastatic involvement, and prognostic risk factors such as time from diagnosis to treatment and laboratory findings. Due to the limited number of cases in the literature, it is impossible to establish a standard treatment protocol or gain definitive prognostic information for RCC patients with thyroid and bilateral adrenal metastases. Therefore, it is crucial to be vigilant for metastases in the follow-up of RCC patients, even years after radical nephrectomy.

REFERENCES

1. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, Gore JL, Sun M, Wood C, Russo P. Epidemiology of Renal Cell Carcinoma. European urology. 2019; 75(1):74-84.
2. Nisi M, Izzetti R, Graziani F, Gabriele M. Renal Cell Carcinoma Metastases to the Oral Cavity: Report of 2 Cases and Review of Literature. Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons. 2020; 78(9):1557-1571.
3. Lopez-Beltran A, Carrasco JC, Cheng L, Scarpelli M, Kirkali Z, Montironi R. 2009 update on the classification of renal epithelial tumors in adults. International journal of urology: official journal of the Japanese Urological Association. 2009; 16(5):432-43.
4. Iesalnieks I, Trupka A, Raab M, Glockzin G, Woenckhaus M, Schlitt HJ, Agha A. Renal cell carcinoma metastases to the thyroid gland-8 cases reported. Thyroid: official journal of the American Thyroid Association. 2007; 17(1):49-52.

5. Karadağ D, Çağlar O. İki taraflı sürrenal metastazlı renal hücreli karsinom olgusu. Türk Üroloji Dergisi/Turkish Journal of Urology. 2011; 37(1): 67-70.
6. HooKim K, Gaitor J, Lin O, Reid MD. Secondary tumors involving the thyroid gland: A multi-institutional analysis of 28 cases diagnosed on fine-needle aspiration. Diagnostic cytopathology. 2015; 43(11):904-11.
7. Aljiabri KS, Bokhari SA, Fadag RB, et al. Thyroid metastasis from renal cell carcinoma, Archives of endocrinology and diabetes care. 2018; 1:65-70.
8. Bohn OL, De las Casas LE, Leon ME. Tumor-to-tumor metastasis: Renal cell carcinoma metastatic to papillary carcinoma of thyroid-report of a case and review of the literature. Head and neck pathology. 2009; 3(4):327-30.
9. Romero Arenas MA, Ryu H, Lee S, Morris LF, Grubbs EG, Lee JE, Perrier ND. The role of thyroidectomy in metastatic disease to the thyroid gland. Annals of surgical oncology. 2014; 21(2):434-9.
10. Chung AY, Tran TB, Brumund KT, Weisman RA, Bouvet M. Metastases to the thyroid: a review of the literature from the last decade. Thyroid: official journal of the American Thyroid Association. 2012; 22(3):258-68.
11. Li Y, Ji Z, Wang D, Xie Y. Bilateral adrenal metastasis of renal cell carcinoma 4 years after radical nephrectomy: A case report and review of literature. Medicine (Baltimore). 2021; 100(31):e26838.
12. Utsumi T, Suzuki H, Nakamura K, Kim W, Kamijima S, Awa Y, Araki K, Nihei N, Naya Y, Ichikawa T. Renal cell carcinoma with a huge solitary metastasis to the contralateral adrenal gland: a case report. International journal of urology: official journal of the Japanese Urological Association. 2008; 15(12):1077-9.
13. Machens A, Dralle H. Outcome after thyroid surgery for metastasis from renal cell cancer. Surgery. 2010;147(1):65-71.
14. Beutner U, Leowardi C, Bork U, et al. Survival after renal cell carcinoma metastasis to the thyroid: single center experience and systematic review of the literature. Thyroid. 2015;25(3):314-324.
15. Iesalnieks I, Winter H, Bareck E, et al. Thyroid metastases of renal cell carcinoma: clinical course in 45 patients undergoing surgery. Assessment of factors affecting patients' survival. Thyroid. 2008;18(6):615-624.

Osmangazi Journal of Med, 2025;47(1): 163-175
DOI: 10.20515/otd. 1564871

Review
Derleme

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Afterloading Brakiterapi Sistemlerinde Kaynak Kalibrasyonu ve Radyasyon Güvenliği

Source Calibration and Radiation Safety in Afterloading Brachytherapy Systems

Nural Öztürk

Aydın Adnan Menderes University Faculty of Medicine, Department of Radiation Oncology, Aydın, Türkiye

ORCID ID of the authors
NÖ. 0000-0002-7405-2693

Correspondence / Sorumlu yazar:
Nural ÖZTÜRK

Aydın Adnan Menderes University Faculty of Medicine, Department of Radiation Oncology, Aydın, Türkiye

e-mail: nural.ozturk@adu.edu.tr

Abstract: Brachytherapy helps to deliver radiation directly to the location of cancer cells through the placement of small radioactive sources inside the body. Today, irradiation with it is considered an essential part of treatment for almost all cancerous areas. Based on the improved localization techniques and treatment planning systems, it is now possible to have precise and reproducible dose distributions. In therapeutic applications, doses are high and deviation from the prescribed level can lead to serious or even fatal consequences. However, the desired clinical results can be achieved only with good clinical and dosimetric practice, in other words, with the comprehensive Quality Assurance (QA) program implementation that includes detailed Quality Control procedures. The most basic element in QA can be achieved by determining the source information accuracy. One of the most necessary elements for source calibration works correctly by means of the equipment that is needed for this calibration according to the existing setup in the center (well-type ion chamber, jig phantom, special calibration phantom, suitable ion chambers, and electrometers). In addition, among the necessary duties for QA are the determination of the task's distribution, responsible persons' authorization, and appropriately training of all relevant personnel. In addition, the existence of a center-specific quality control and radiation safety procedure is the basis for correct and high-quality practices.
Keywords: Brachytherapy, radiation, radiation protection, quality control and assurance

Informed Consent: No informed consent was needed for this review.
Copyright Transfer Form: Copyright Transfer Form was signed by the authors.
Authorship Contributions: Data collection and writing; NÖ design, literature review, writing and supervision; NÖ
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.
Funding: This study has not any funding.

Özet: Brakiterapi, kanserli hücrelerin bulunduğu yere doğrudan ışın verebilmek için radyoaktif kaynakların doku içi, vücut yüzeyi ve boşluklarına yerleştirilerek yapılan tedavidir. Günümüzde, brakiterapi ile ışınlama, neredeyse tüm kanser bölgeleri için tedavinin temel bir parçası olarak kabul edilmektedir. İyileştirilmiş lokalizasyon teknikleri ve tedavi planlama sistemleri ile artık hassas ve tekrarlanabilir doz dağıtımına sahip olmak mümkündür. Terapötik uygulamalarda dozlar yüksektir ve reçete edilen dozdan sapma ciddi veya hatta ölümcül sonuçlara yol açabilir. Yüksek dozlar lokal olarak hedefe verilirken çevredeki normal dokularda hızlı doz düşüşü sağlanır. Küçük hacimlerde kısa sürede yüksek doza ulaşıldığı için kalite kontrolü oldukça önemlidir. Ancak, istenen klinik sonuçlar yalnızca iyi bir klinik ve dozimetrik uygulama ile, yani kısaca ayrıntılı Kalite Kontrol prosedürlerini içeren kapsamlı, uygulanabilir ve tekrarlanabilir bir Kalite Güvence (KG) programının uygulanmasıyla elde edilebilir. Bu KG' nin en temel unsurlarından birisi de kaynak bilgilerinin doğruluğunun tespit edilmesi ve Tedavi Planlama Sistemine (TPS) girilmesidir. Bu kalibrasyon için merkezde mevcut olan düzeneğe göre ihtiyaç duyulan ekipmanların (Kkuyu-tipi iyon odası, jig fantom, özel kalibrasyon fantomu, uygun iyon odaları ve elektrometreler) doğru çalışıyor olması kaynak kalibrasyonu için en gerekli unsurlardan biridir. Ayrıca görev dağılımının belirlenmesi, sorumlu olacak kişilerin yetkilendirilmesi, ilgili tüm personelin görevleri için uygun şekilde eğitilmesi KG için gereklidir. Bunlara ilave olarak merkeze özgü kalite kontrol ve radyasyon güvenliği prosedürünün mevcudiyeti doğru ve kaliteli uygulama yapmanın temelidir.
Anahtar Kelimeler: Brakiterapi, radyasyon, radyasyondan korunma, kalite kontrol

Received 11.10.2024
Accepted : 20.12.2024
Published :.30.12.2024

How to cite/ Atıf için: Öztürk N, Afterloading Brakiterapi Sistemlerinde Kaynak Kalibrasyonu ve Radyasyon Güvenliği, Osmangazi Journal of Medicine, 2025;47(1):163-175.

1. Giriş

Kanser, küresel çapta önde gelen ölüm nedenlerinden biridir. Dünya Sağlık Örgütü (*World Health Organization*-WHO), 2012 yılında 7,6 milyon kişinin kanserden öldüğünü ve ölümlerin oranlarının artmaya devam ettiğini bildirmiştir (1). 2025 yılına kadar bu sayının yıllık 11,4 milyona ulaşacağı tahmin edilmektedir. WHO'ne göre kanserle ilişkili tüm ölümlerin %70'inden fazlasının, önleme, teşhis ve tedavi kaynaklarının sınırlı veya hiç olmadığı düşük ve orta gelirli ülkelerde (LMIC'ler) meydana gelmektedir. Ayrıca yüksek gelirli ülkelerde, kanser vakalarının yaklaşık %50'sinin en az bir kere radyoterapi ile tedavi edildiği belirtilmektedir. WHO verilerine göre, düşük ve orta gelirli ülkelerde kanser tanısı konulduğundaki vakaların ileri düzeyde olması ve kaynak eksikliği nedeniyle, radyoterapi gerektiren vaka sayıları gelişmiş ülkelere göre daha yüksektir. Global bazda düşük doz oranlı ekipmanların sınırlı üretiminin durdurulması, düşük ve orta gelirli ülkelerden Yüksek Doz Oranlı (High Dose Rate= HDR) brakiterapi ekipmanlarına olan talebin artmasına neden olmuştur. Ayrıca, WHO bültenlerinde brakiterapi ile tedavi için uygun olan bazı kanser türlerinin (serviks, özofagus ve nazofarenks) düşük ve orta gelirli ülkelerde daha sık görüldüğünden bahsedilmektedir (1).

Curie'ler tarafından 1898'de radyoaktif radyumun keşfedilmesinden beş yıl sonra Radyum (Ra) -226, brakiterapide başarıyla kullanılmaya başlandı (2). Sonraki 50 yıl boyunca radyum, brakiterapi uygulamaları için tercih edilen izotop oldu ve sonrasında çok daha kısa yarı ömürlere sahip kobalt, sezyum ve iridyum gibi reaktörde üretilen radyo-nüklitlere yerini bırakmıştır. Günümüzde, brakiterapi ile ışınlama, neredeyse tüm kanser bölgeleri için tedavinin temel bir parçası olarak kabul edilmektedir (3).

Brakiterapi (BT), kapalı bir radyoaktif kaynağın interstisyel, intrakaviter, intraluminal veya yüzey uygulamasıyla radyasyonu iletmek için kullanıldığı manuel ve afterloading olarak uygulanabilen terapötik radyasyon tedavi yöntemidir. Afterloading tekniğinde, aplikatörler hastaya yerleştirildikten sonra radyoaktif kaynaklar aplikatöre uzaktan kumanda ile sonradan yüklenmektedir. Bunun amacı uygulama sırasında çalışan maruziyetini azaltmaktır. Brakiterapide kanserli doku ve hücreler hedef hacimden kısa bir mesafede küçük kapsüllü radyoaktif kaynaklarla ışınlanır (4). Doğru kaynak yerleşimi brakiterapi ile iyi sonuçlar elde etmek için en önemli faktördür (5).

Işınlanan hacim ile sağlıklı doku komplikasyon olasılığını değerlendiren tedavi modellemeleri, ışınlanan hacim ile komplikasyon riski arasında bağlantı olduğunu kabul ederler (6,7).

BT'de tanımlanan klinik target volüm (CTV), planlanan target volüm (PTV) ile aynı olduğundan eksternal RT'ye göre hedeflenen hedef volüm belirgin olarak küçüktür. Uluslararası Radyasyon Birimleri ve Ölçümleri Komitesi(International Commission on Radiation Units and Measurements, ICRU), ICRU 50 (1993) (8), ve ICRU 62 (1999) (9) protokollarına göre target volüm tanımlamalarında dozun verildiği izodoz %95–107 aralığındadır. -%5 ve +%7 aralığındaki sapmalar homojen kabul edilir. Brakiterapide ise küçük bir hacim son derece heterojen bir doz dağılımı ile tedavi edilir. Tümör bölgesi yüksek doza maruz kalırken, hızlı doz düşüşü sebebi ile sağlıklı dokular ve kritik organlar (mesane, rektum) daha iyi korunmaktadır.

a) Brakiterapide kullanılan kaynak tanımlamaları

Radyoaktif kaynaklar, kaynak aktivitelerine göre düşük doz hızı, orta doz hızı ve yüksek doz hızı olarak tanımlanır. Kanser tedavilerinde son yıllarda sıklıkla HDR kaynaklar kullanılmaktadır. Brakiterapi tedavileri primer tedavi olarak uygulanabildiği gibi, eksternal radyoterapi sonrası ek tedavi (boost) tedavi veya cerrahi ve kemoterapi gibi diğer terapilerle birlikte kullanılabilir (10-12). ICRU 38. raporunda (11), brakiterapi uygulamalarını doz hızına göre 3 kategoriye ayırmıştır (12,13).

- Düşük Doz Hızlı (Low Dose Rate: LDR): Kaynak doz hızı 0.4–2 Gy (Gray) / saat dir. Klinik uygulamalarda genellikle 0.4–1 Gy/saat aralığında doz hızları kullanılır. LDR kaynaklar manuel ya da otomatik afterloading sistemleri ile uyumludur.
- Orta Doz Hızlı (Medium Dose Rate: MDR) nin doz hızı 2–12 Gy/saat arasındadır. Manuel ya da otomatik afterloading sistemler ile verilebilir. Bununla birlikte modern uygulamalarda çok nadir kullanılır.
- Yüksek Doz Hızlı (High Dose Rate: HDR) kaynakların doz hızı ≥12 Gy/ saat >20 cGy/dk'dır. Son yıllarda brakiterapi uygulamalarında sıklıkla kullanılmaktadır

- Kaynak aktivitesi çok yüksek olduğundan sadece afterloading yükleme ile uygulanır.

Son yıllarda cerrahi işlemle, anestezi altında manuel kalıcı "seed"ler kullanılarak uygulanan brakiterapiler ise çok düşük doz hızlı (Very Low Dose Rate: VLDR) brakiterapi olarak adlandırılır. Bu kaynaklar <0.4 Gy/saat gibi çok düşük bir doz hızına sahiptir. HDR brakiterapi uygulamaları için en önemli referans protokolleri için Amerikan Tıp Fizikçileri Derneği (American Association of Physicists in Medicine, AAPM) Task Grup Rapor 59 (13), Task Grup Rapor 56 (2) ve Task Grup Rapor 40 dikkate alınmaktadır (14). Sistem kurulumlarında ve hasta alımları sırasında dikkat edilmesi gereken kural ve tavsiyeler bu referanslardan yararlanarak elde edilebilir.

Bu çalışmanın amacı; brakiterapide kullanılan kaynakların, aktivitelerinin doğruluğunu hangi yöntemlerle kontrol edilebilirliğini örneklerle açıklayarak, kaynak güvenliğini içeren yaptırımları araştırmaktır.

b) Brakiterapinin Amacı

Brakiterapi uygulamanın amacı, kullanılan iyonize radyasyon kaynaklarının sadece yakın çevresinindeki alanı etkilemesidir. Doz kaynaklara yakın bölgede hayli yüksekken, kaynaktan çevreye doğru uzaklaştıkça hızla (uzaklığın karesi ile ters orantılı olarak) düşer. Bu da sağlıklı kritik organ dozlarının korunması anlamına gelmektedir. Ayrıca, hasta hareket ederse veya tedavi sırasında tümörün vücut içinde herhangi bir hareketi olursa bile radyasyon kaynakları tümöre göre doğru pozisyonlarını korur. Brakiterapinin bu özelliği, Eksternal Radyoterapi (EBRT)'ye göre avantajlar sağlar. BT uygulamaları sırasında tümör bölgesi yüksek dozlarla ışınlanırken, hızlı doz düşüşü nedeni ile çevredeki sağlıklı dokular gereksiz radyasyona daha az maruz kalır(5, 6, 15).

Fraksiyonlar halinde uygulanan Brakiterapi tedavileri diğer radyoterapi tekniklerinden daha kısa sürede tamamlanabilir. Bu, hayatta kalan kanser hücrelerinin her radyoterapi dozu arasındaki aralıklarda bölünüp büyüme şansını azaltmaya yardımcı olur (16). Ayrıca harici radyoterapi (EBRT) ile karşılaştırıldığında fraksiyonlar az olduğu için merkeze gelişler az ve tedavi ayaktan hasta olarak tamamlanabilmektedir. Bu, tedaviyi birçok hasta için erişilebilir ve kullanışlı hale getirir (17,18).

c) Kalite Güvencesinin Gerekliliği

HDR brakiterapilerde çok yüksek aktiviteye (10 Curie (Ci)) sahip kaynaklar kullanılır. Gerekli dozimetrik ve planlama ekipmanını kullanarak KG prosedürlerini, uygulayacak eğitimli bir ekibin olması son derece önemlidir**.** KG, mümkün olan en iyi tümör kontrolünü elde etmek, gereksiz yan etkilerden kaçınmak ve HDR BT'yi doğru ve güvenli bir şekilde gerçekleştirmek için gereklidir. KG son derece önemlidir, çünkü HDR BT uygulamaları kısa bir sürede hızlı bir şekilde gerçekleştirilir. Bu uygulama esnasında kısa bir zaman diliminde yüksek dozlar verilir ve düzeltme için çok az fırsat vardır (1). Günümüzde, brakiterapi ile ışınlama, neredeyse tüm kanser bölgeleri için tedavinin temel bir parçası olarak kabul edilmektedir. İyileştirilmiş lokalizasyon teknikleri ve tedavi planlama sistemleri ile artık hassas ve tekrarlanabilir doz dağıtımına sahip olmak mümkündür. Radyasyon terapisindeki amaç iki yönlüdür: tümör kontrolü için yeterli olan ancak aynı zamanda normal dokulardaki komplikasyonları en aza indiren bir doz ve doz dağılımı sağlamak. Ancak, istenen klinik sonuçlar yalnızca iyi bir klinik ve dozimetrik uygulama ile gerçekleşebilir. Bu da ayrıntılı Kalite Kontrol prosedürlerini içeren kapsamlı bir KG programının uygulanmasıyla elde edilebilir. Brakiterapide KG konusunda kullanılabilecek, pratik çözümler sunan referanslar mevcuttur (16-19).

Bu referanslar kullanılarak merkeze özgü kapsamlı kalite güvence programı oluşturmak mümkündür. Mevcut BT gurup raporlarında da özetlendiği gibi, brakiterapi uygulamalarındaki kazalar, kaynakların izlenebilir kalibrasyonunun olmaması, miktarların ve birimlerin yanlış kullanılması veya doz hesaplama prosedüründe yapılan hatalar nedeniyle meydana gelmektedir.

Kalite kontrol programının genel amacı, kabul testleri tamamlanmış ve klinik kullanım için hazır halde bulunan bir sistemin zamana ve kullanıma bağlı olarak başlangıçtaki standartlara göre karşılaştırılması ve rutin klinik uygulamalarda kullanım için hazır halde bulundurulmasıdır (20).

d) Brakiterapi Kalite Kontrolunda Kaynak Kalibrasyonunun Önemi

Uygulama karmaşıklığı ve hassasiyetine ek olarak radyoaktif kaynak kullanımından dolayı, hem hastanın doğru tedavisi hem de hastaların, hastane çalışanlarının ve toplumun radyasyon güvenliği açısından brakiterapide rutin kalite kontrol programının titizlikle uygulanması çok önemlidir.

Kalite temininin sürdürülebilir olması için programın sorumlu medikal fizik uzmanı tarafından ölçüm periyotlarını ve yöntemlerini de içerecek şekilde belirlenmesi ve her kontrol sonunda ölçülen sonuçların dokümantasyonu gerekmektedir.

Genel olarak kalite kontrol programı kapsamında yapılması gereken testler iki grupta toplanabilir: Mekanik ve dozimetrik testler. Mekanik testler, cihazın özelliklerine bağlı olarak fiziksel parametrelerin kontrolü ve güvenlik sistemlerinin kontrolleridir. Dozimetrik testler ise her kaynak değişiminde, radyoaktif kaynağın aktivitesinin ölçülmesini ifade eder.

HDR Brakiterapilerde sıklıkla kullanılan kaynak İridyum-192 (Ir-192) kaynağıdır. Ir-192, 73,827 günlük bir yarı ömre sahip olan iridyumun radyoaktif bir izotoptur. Radyoaktif bozunmasını ve radyobiyolojik etkisini de göz önüne alarak kaynağın tedavide her üç ila dört ayda bir değiştirilmesi gerekmektedir. Her merkez bölüme özgü (merkezde mevcut olan cihaz, kalibrasyon fantomları kuyu tipi veya farmer tipi iyon odaları vb.) uygun mevcut ölçüm aletlerinden yararlanarak kalite kontrol prosedürleri hazırlamalıdır. Ayrıca hazırlanan prosedürlerden yararlanarak KG programı tasarlanmalıdır. Brakiterapi uygulamaları yapan merkezler, farklı bir yarı ömre ve dolayısıyla farklı bir değişim aralığına sahip kaynaklar için, yılda en az üç kez kapsamlı bir KG test sıklığı gerçekleştirilmelidir.

2. Tartışma

Brakiterapi Sistemlerinde Kaynak Test ve Kalibrasyonu

Sonradan yüklemeli HDR brakiterapi sistemlerinde sıklıkla Ir-192 kaynağı kullanılır. Bütün testler önemli olsa da kaynak testleri ve özellikle aktivite testi tedavi doğruluğu açısından büyük önem taşımaktadır. Brakiterapi dozimetrisi için KG programının önemli bir parçası kaynak kalibrasyonudur. Bazı brakiterapi kaynakları için, satıcılar belirtilen kalibrasyon değerlerin de ±%10'a kadar belirsizlikler bildirir. Brakiterapi kaynaklarının son kullanıcı kalibrasyonu, yalnızca satıcının belirttiği kalibrasyonu kontrol etmek için değil, aynı zamanda uluslararası kabul görmüş standartlara göre izlenebilirliği sağlamak için de gereklidir. Afterloader'ın sızıntı radyasyonu güvenli bir cihaz için 0,1 m mesafedeki doz hızı 1 μSv/h'dir (mikro sievert/saat) (21,22).

a) Kirlenme testi

Brakiterapi kaynağı ilgili ilk yapılacak uygulama kirlenme testidir. Kirlenme testi sırasında; Kaynak, kaynak kablosu, sahte ve sahte kablo radyasyon kirliliğinden arındırılmış olmalıdır. Maksimum doz seviyeleri ulusal düzenlemelerde ve ayrıca afterloader cihazı ile birlikte gelen dokümanda belirlenmiştir. Hem eski hem de yeni kaynakta silme testi ile kaynak değişimi gerçekleştirilir (18,19).

b) Referans Air Kerma (RAKR) Testi

Her yeni kaynak ile birlikte Referans Air Kerma (RAKR) belirten doz değeri, kaynak üreticisinden bir sertifika ile birlikte gelir. Bu sertifika kullanılarak, ölçüm ile bu RAKR değerinin doğruluğu ölçülerek tespit edilir. Kaynak değişiminden sonra ve klinik kullanımdan önce kaynak aktivite değeri yerel protokole göre ölçülmeli ve sertifikada belirtilen değerle karşılaştırılmalıdır. ICRU raporları 38 (11) ve ICRU 58 (23) brakiterapi kaynaklarının dozimetrik olarak kontrol edilmesini önermektedir**.**

Kaynak sertifikası

Ölçülen değer, belirtilen değerden % 5'ten fazla saptığında veya sertifikası olmayan kaynaklar kesinlikle klinik kullanıma alınmamalı ve kaynak üretici firma ile iletişime geçilmelidir. Ayrıca ölçüm sonucunda tespit edilen %3'ten büyük tutarsızlıklar araştırılmalıdır (18,24). Kaynak aktivitesi, her kaynak değişiminden sonra ölçülüp kaynak sertifika değeri ile karşılaştırılıp tedavi planlama bilgisayarına girilmelidir. HDR brakiterapi kaynaklarının aktivite ölçümünde kullanılan iki referans protokol Uluslararası Atom Enerjisi Ajansı (IAEA) tarafından yayınlanan Tec Doc 1274 (22) ve Tec Doc 1079 numaralı raporlardır (25).

Üç farklı yöntem kullanılarak kaynak aktivitesi ölçülür (18,19,26).

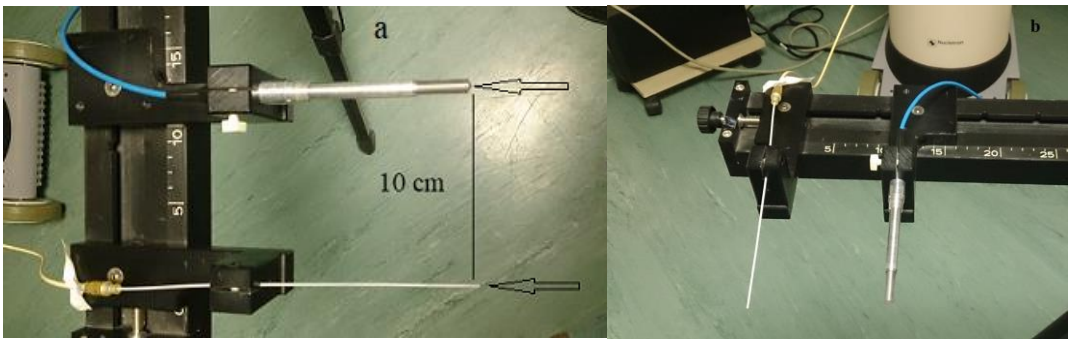
Aktivite ölçümü

- Havada iyon odası ile ölçüm
- Kuyu tipi iyon odası ile ölçüm
- Özel fantomlar ile ölçüm

1) Havada iyon odası ile ölçüm

Kaynak gücünü ifade etmek için kullanılan nicelik hava kerma gücüdür. Birim zamandaki hava kerma hızı olarak tanımlanır. HDR brakiterapi kaynakları

için kullanılan birimi µGy (mikro gray) /h'tir. HDR brakiterapi kaynakları için üretici tarafından kaynak sertifikasında verilen değer görünür kaynak aktivitesidir (A_{app}). Havada iyon odası ile ölçümde kullanılması önerilen iyon odaları 0,6cc hacimli Farmer tipi iyon odalarıdır.



Resim 1. a) Havada Brakiterapi kaynak ölçümü için özel üretilmiş kalibrasyon jig'i **b)** jig üzerine ölçüm sisteminin konumlanması.

Bu iyon odaları ile kullanılacak elektrometrelerin mutlaka İkincil Standart Dozimetri (Secondary Standard Dosimetry Laboratory, SSDL) laboratuvarlarında, ülke protokolüne göre belli periyotlarda kalibre edilmiş olması gerekmektedir. Ölçüm için özel üretilmiş kalibrasyon jig'leri de mevcuttur. Ölçüm sırasında iyon odası çevresinde metal herhangi bir şeyin olmamasına ve yerden gelecek saçılmalar göz önüne alınarak yerden yüksekte ölçüm düzeneğinin kurulması gerekir (Resim 1a,b). Pozisyonlama belirsizliğini ve kalibrasyon jigi saçılma faktörün azaltmak için kaynak iyon odasının geometrik orta noktasına gelecek şekilde, ölçüm uzaklığı ise plastik katater ve iyon odası arasındaki mesafe 10cm olacak şekilde ayarlanır (21).

Barometre ve termometrenin ortama uyum sağlayabilmesi için en az bir saat önce ölçüm yapılacak olan odaya konulması gerekir. Elektrometre ve iyon odası bağlantısı yapılıp 60 sn'lik sürede elektrometreden elde edilen okuma değeri IAEA-Tec Doc-1079 ve IAEA-Tec Doc-1274'te belirtildiği üzere Denklem1 ve Denklem2'de yerine konarak kaynak aktivitesi bulunur (22,25-28).

$$K_R = N_K \,.\, (M_u / t).\, K_{air} \,.\, k_{scatt} \,.\, k_n \,(\, d / d_{ref}\,)^{\,2} \qquad (1)$$

$$\text{Aktivite} = K_R / (\Gamma_\delta) \,.\, (\,W/e)_{air} \qquad (2)$$

Denklemde,

K_R = Kaynağın referans hava kerma oranı

N_K = Gerçek foton enerjisinde iyonizasyon odasının hava kerma kalibrasyon faktörü

M_u = "t" süresinde toplanan ve kaynak transferi sırasında ortam sıcaklığı ve basıncı, rekombinasyon kayıpları ve geçiş etkileri için düzeltilen ölçülen yük.

t = Kaynak başlangıcından itibaren geçen zaman

K_{air} = Hava azaltma düzeltmesi

k_{scatt} = Oda Saçılma Faktörü

k_n = Gradient Faktörü

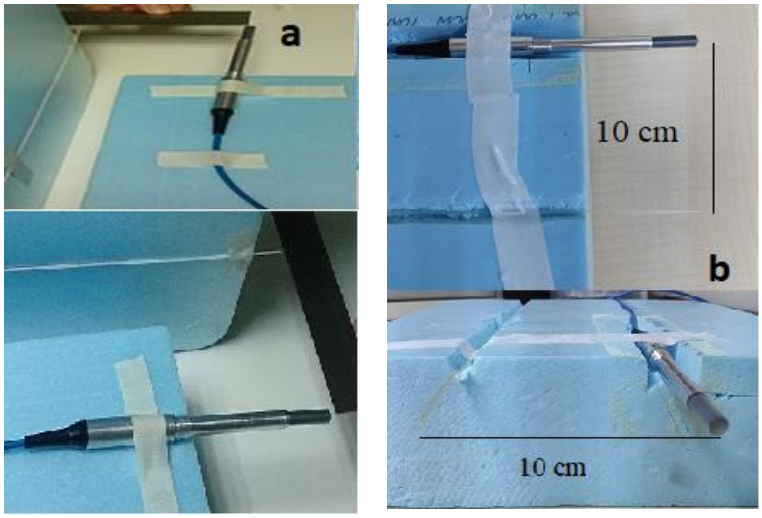
d = Ölçüm mesafesi, yani kaynağın merkezi ile iyonizasyon odasının merkezi arasındaki mesafedir

d_{ref} = Bir metrelik referans mesafesi

Γ_{δ} = Referans Hava Kerma

$(W/e)_{air}$=Havada tek iyon çiftini üretmek için ihtiyaç duyulan ortalama enerji (8,730 mGy/R(miliGray/Röntgen)) göstermektedir.

Eğer merkezde özel jig fantomu yoksa strafor köpük üzerine iyon odası ucu dışarda kalacak şekilde farmer tipi iyon odası sabitlenir. 10 cm yanına kaynak Kalite Kontrol (Quality Assurance- QA) aplikatörü konumlandırılır. 10 cm iyon odası merkezi ile aplikatörün merkezi arasındaki mesafedir. İyon odası kaynak merkezi eksene dik konumda ve iyon odası efektif kaynaklar yerine paralel olmalıdır.



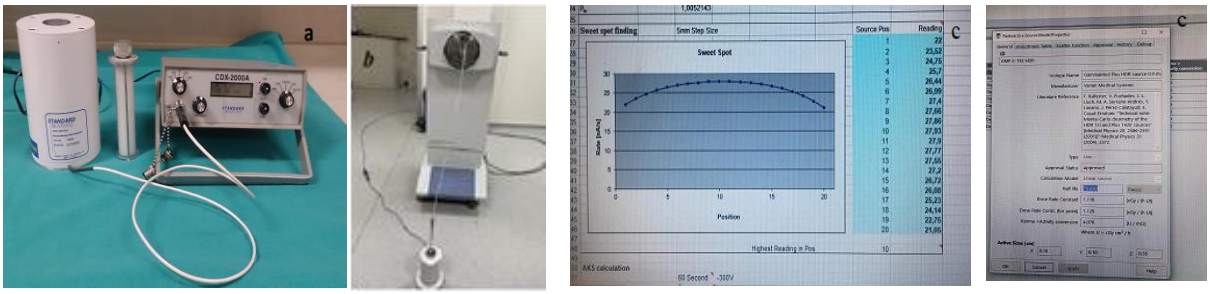
Resim 2. a) İyon odası ve QA aplikatörü strafor köpüğün üzerine (Resim Med Fiz Uz. Halil Küçücük). b) İyon odası ve QA aplikatörü strafor köpüğün içine gömülerek konumlandırma sağlanabilir.

Bu düzenekle ölçüm alınırken konumlandığı yer, saçılmaya sebep verebilecek yapılardan arındırılmış (metal aksamdan ve yerden yeterince uzak) olmalıdır**.** Resim 2a, b'de farklı ölçüm düzenekleri görülmektedir.

2) Kuyu Tipi İyon Odası ile Ölçüm

Brakiterapi kaynak kalibrasyonları için kuyu tipi oda (Resim 3a), hem LDR hem de HDR kaynaklarının RAKR ölçebilen radyoterapi uygulamaları için özel olarak tasarlanmış tipte olmalıdır. Sadece atmosfere açık kuyu tipi odaların kullanılması tavsiye edilir. Hazne sızdırmaz hale getirilmişse ve gazın basıncı ortamın atmosfer basıncından daha yüksek bir seviyede ise, gazın yavaş sızması sorunu gelişebilir. Bu durumda, kalibrasyon faktöründe bir değişiklik meydana gelir. Atmosfere açık odaların sıcaklık ve basınç için düzeltmeye ihtiyacı vardır, çünkü kalibrasyon faktörü, genellikle 20 C^{o} ve 101,3 kPa (kilopaskal) olmak üzere standart ortam koşullarına karşılık gelen hava yoğunluğuna dayanır. Odalar sadece aktivite birimlerinde ölçülür. Kuyu tipi oda ve elektrometrenin bağımsız kalibrasyon faktörlerine sahip olabileceğine dikkat edilmelidir. Bu durumda, kuyu tipi oda ve elektrometre sisteminin toplam kalibrasyon faktörünü oluşturmak için kalibrasyon faktörleri birlikte çarpılmalıdır. Kuyu tipi bir odanın kalibrasyon noktası, kalibrasyon prosedürü sırasında kaynağın merkezinin konumlandığı nokta olarak tanımlanır. Bu nokta, kaynak uzunluğuna bağlı olarak bir kaynaktan diğerine farklılık gösterebilir. Bazı odalarda kuyuda sabit, çıkarılamayan bir ara parçası bulunur ve kaynak uygulama sırasında, uygun şekilde ara parçanın üstüne yerleştirilir. Diğer modellerde ise kaynak tutucuyu farklı yüksekliklere hareket ettirilip-sabitlemek için hareketli mekanizma bulunur. Kalibrasyon işlemleri sırasında kaynak daha sonra hareketli tutucunun altına yerleştirilir. Kalibrasyon noktasının konumu, iyon odasının

kalibrasyon sertifikasında belirtilmiş olması gerekir (22,23) .



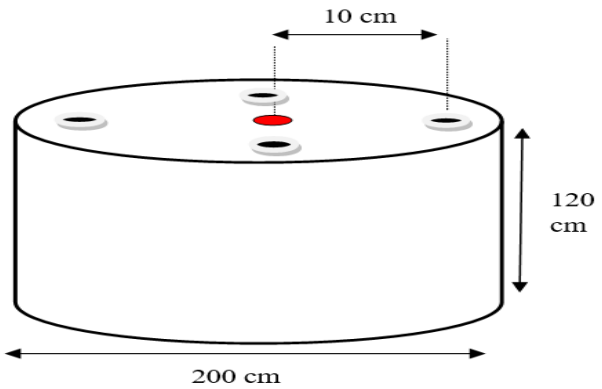
Resim 3. **a)** Kuyu tipi iyon odası **b**) kuyu tipi iyon odası ölçüm set-up pozisyonu **c)** Etkin kaynak yeri tespiti (22,25).

Ölçüm için, kaynak transfer kablosu ile kuyu tipi iyon odası ve elektrometre bağlantısı yapılır (Resim 3b). Barometre ve termometrenin ortama uyum sağlayabilmesi için en az bir saat önceden ölçüm yapılan odaya konulması gerekmektedir. Dikkat edilmesi gereken nokta, iyon odasının en yüksek sinyali verdiği ölçüm mesafesinin belirlenmesidir (Resim 3c). Ayrıca ara transfer kablolarının mümkün olduğu kadar düz hat üzerinde olmasına gayret edilmesi gerekir. Çoklu ölçümler alınarak maksimum okuma değeri ve pozisyonu bulunur. 1cm duruşlar ile 10 okuma değeri alınır.

En yüksek değerin okunduğu mesafenin olduğu aralıkta 0,5 cm duruşlar ile ardaşık 10 okuma alınır. Okuma aralığı daraltılarak 0,2 cm duruş aralığı ile 10 okuma alınarak en yüksek okuma değeri ve pozisyonu hassas olarak belirlenir. Basınç, sıcaklık ve en yüksek okuma değerleri ile birlikte aktivite hesaplanır ve sertifika değeri ile karşılaştırılır. Fark % 5 in içerisinde olmalıdır (17,21,22).

3) Özel Fantomlarla Ölçüm

Kaynak aktivitesi, iyon odası, elektrometre ve silindirik katı fantom kullanılarak ölçülebilir. Silindirik fantomun geometrisi merkezde kaynağın gideceği kateter kanalı ve kanal çevresinde birbirine dik açı ile (0^0, 90^0, 180^0, 270^0) konumlanmış dört kanaldan oluşur (Resim 4). Kateter çevresindeki dört kanala iyon odasını sırayla yerleştirip 60 sn'lik okumalar alınır. Tüm geometrideki okumaların ortalaması alınıp aktivite hesaplanır (18,19).



Resim 4. Silindirik PMMA özel fantomun şematik gösterimi**.** Radyoaktif Ir-192 kaynağı merkezi eksendeki kırmızı ile gösterilen kaynak kalibrasyon aplikatörüne uygun yere yerleştirilmektedir. Çevredeki siyahla gösterilen 10 cm uzaklıktaki 4 delik iyon odası girişini göstermektedir.

Merkezlerin imkanları doğrultusunda yukarıda tanımlanan farklı düzeneklerden, uygun olan ölçüm düzeneği kullanılarak kaynağın aktivite değeri tespit edilir. Bunun için Türkiye Cumhuriyeti Fizik

Mühendisleri Odası- Kalite Uygunluk Belgesi (TC FMO-KUB) dökümanlarında aktivite tayini maddesindeki Tablo 1 örnek olarak kullanılabilir. Örnek olarak Tablo 1 de Elektrometre olarak Standart Imaging CDX-2000B ve İyon Odası olarak Extradin-A19 kullanılarak yapılan ölçümler referans alınarak Denklem(3), Denklem(4), Denklem(5), Denklem(6), Denklem(7)'den yararlanarak nasıl hesap yapıldığı ayrıntılı anlatılmıştır.

$$Hava\ Kerma(HK)$$

$$(HK) = Mu * Nk(Ir-192) * kair * kscatt * kn * Ctp \quad (3)$$

HK= 0,70 * 45,428* 1,001*1*1,009*1,01473 = 32,5909

$$Basınç - sıcaklık\ düzeltmesi(Ctp)$$

$$(Ctp) = \{273.2 + T/273.2 + 20\} * \{1013/P\} \quad (4)$$

SERTİFİKA BİLGİLERİ

Tablo 1. Aktivite Tayini	
Üretici Firma	
Kaynak	Iridium -192
Ölçüm Tarihi	24.05.2012
Referans Hava Kerma	
Yarı Ömür - Aktivite	73,8 gün
Sertifikada belirtilen ölçüm tarihine göre geçen süre (kaynakla birlikte gelen fabrikadaki kaynak aktivite raporundan temin edilir)	109 gün
Bozunma Faktörü	0,3593

ÖLÇÜM BİLGİLERİ

TARİH :	
Elektrometre : Standart Imaging CDX-2000B	İyon Odası: Extradin - A19
Fantom	Havada build-up cap
Basınç : 1016 mBar Sıcaklık: 25,5ºC	Ctp :1,01473
Nk (Co-60 (iyon odası ve dozimetrenin birbirlerine göre SSDL kalibrasyonu)	45,428 mGy/nC
Nk (Ir-192)	1.007
k_n (Gradient Faktörü)	1.009
k_{scatt} (Oda Saçılma Faktörü)	1
k_{air} (hava azaltma düzeltmesi)	1.001
Ölçüm mesafesi	10 cm
Ölçüm Zamanı (t) s	60 s
OKUMA (nC)	0,70nC
RHK (Referans Hava Kerma)	
$(\Gamma_\gamma)_x$ (Ir-192)	0.4658 R m^2/hCi^{-1}
$(\Gamma_\gamma)_x$(Co-60)	1.307 R m^2/hCi^{-1}
Ölçülen Aktivite (Ci)	4,789 Ci Fark= %2,1
Ölçülen / Sertifika (%)	4,789 / 4,6889 = %2,1

HK= Hava Kerma

C_{tp} = 1,01473 (Basınç,sıcaklık faktörü)

Mu^{o} = 0,70 nC T= 25,5 Sıcaklık (C^{o}) P= 1016 mBar

$$ReferansHavaKerma(RHK) = \frac{HK*60}{100} = 19{,}554 \quad (5)$$

$$Aktivite = \frac{RHK}{\Gamma\gamma*8{,}764} = \quad (6)$$ 19,554 / 0,4658 * 8,764 = 19,554/4,08227 = 4,789 Ci (Ölçümle bulunan aktivite değeri)

$$A = Ao * e^{-\lambda t} \quad (7)$$ Ao * $e^{-\left(\frac{0{,}693}{73{,}8}\right)*109}$ = 13,05 * 0,3593 = 4,6889 Ci *(Sertifika değerleri kullanılarak bozunma denklemi ile bulunan aktivite değeri)*

Denklem 7 deki ;

Ao= Başlangıçtaki aktivite, t= zaman, $\lambda =$Bozunma sabiti dir.

Kalite Kontrol Programı Test Sıklığı Ve Müdahale Seviyeleri

Hastaların güvenli ve doğru bir şekilde tedaviye girebilmeleri için klinik yoğunluğu göz önüne alınarak uygulanabilir kalite güvence programı oluşturulmalı ve protololler çerçevesinde zamanında titizlikle uygulanmalıdır (15,20).

Brakiterapide Radyasyon Güvenliği ve Emniyet

a) Radyasyon Güvenliği:

Ir-192 ile HDR ve PDR brakiterapisi, yaklaşık olarak 10 Ci 'ye kadar yüksek aktiviteye sahip radyoaktif kaynakları kullanır. Bu kaynaklarla çalışırken radyasyon güvenliğini sağlamak hem çalışan hem de hasta için büyük önem taşımaktadır. Güvenliğin dikkate alınmadığı durumlarda gereksiz radyasyona maruziyet kaçınılmazdır. Radyasyon güvenliği; çalışma ortamı, sızıntı radyasyonu, Afterloader ve acil durum prosedürlerini kapsamaktadır. Uluslararası kuruluşların bu konularla ilgili yayın ve bültenleri mevcuttur (18).

b) Ir-192 kaynaklarıyla çalışma için radyasyon riski analizi

Ir-192 kaynaklarıyla çalışma için radyasyon riski analizi için yapılması gerekenler aşağıda sıralanmıştır (20,24,29) .

İşlemler ve etkinlikler; radyasyon güvenliği gerekliliği ile ilgili 2014 yılında yayınlanan iki çalışma bu konuya açıklık getirmektedir (30,31). Bu rapor tıp, tarım, endüstri, araştırma ve eğitim sırasında radyasyon kullanımı ve geçmiş faaliyetlerden kalan kalıntılar gibi kazalar veya kronik maruziyet durumlarında müdahale dahil olmak üzere tüm uygulamaları kapsamaktadır. Raporda brakiterapi uygulamalarında hasta güvenliği sorumluluğu hükümet, düzenleyici kurum, lisans sahibi veya kayıtlı kişi ve üreticiler arasında paylaştırılmaktadır. Ancak, hastaların korunması ve güvenliği için birincil sorumluluk, radyasyon dozunun uygulanmasından sorumlu Radyasyon Onkolojisi Uzmanına aittir. Rapora göre kurumun uygulamalardan önce tedavi ve kaynak uygulama gerekliliklerini nasıl yerine getirileceği, neler yapılacağı ile ilgili rehberlik sağlayacak kılavuzları oluşturması gerekmektedir.

Sorumluluklar

IAEA raporunda ilk sorumluluk hükümete aittir.

1) Hükümet sorumlulukları; Yasal ve düzenleyici çerçeveyi oluşturmak ve sürdürmek, yönetmelikler ve kılavuzlar oluşturmak ve teftiş ve uygulama eylemleri gerçekleştirmektir. Hükümetler halkı ve çevreyi korumaktır.

2) Düzenleyici kurum sorumlulukları; Uygulamanın yapıldığı ülkeye ait radyasyon güvenliği kurumlarını içermektedir. 2 hedefi vardır.

- İlk hedef, güvenli olmayan uygulamaları ve güvenli olmayan ekipman kullanımını önleyerek halk sağlığı ve güvenliğini korumak.

- İkinci hedef, halk sağlığını ve güvenliğini artıracak güvenli ve etkili uygulamaları ve ekipmanları teşvik etmektir.

Bu uygulama; Yetkilendirme, Gerekçelendirme, Radyasyon Koruması ve Optimizasyonu ile Doz kısıtlamalarını kapsar. IAEA(25)'in ve ICRP'nin 60 numaralı (29) raporunda uygulama sırasında bu maddeler ayrıntısı ile açıklanmıştır. Raporda, Justification, Optimizasyon ve Doz Sınırlamasından oluşan üç ilkesiyle birlikte radyasyondan korunma sistemi daha da kapsamlı hale getirilmiştir. Bu tavsiyelerin başlıca özellikleri (28) ;

- Etkin doz kavramının ve radyasyona maruz kalmanın canlı dokuda Radyobiyolojik olarak meydana getirdiği zararların güncellenmesi;

- Komisyonun radyolojik korunmaya ilişkin üç temel ilkesini benimseyerek, bu ilkelerin iyonize olan radyasyon kaynaklarına nasıl uygulanacağının ve radyasyona maruz kalan bireyler açısından iyonlaştırıcı radyasyonun sağlık üzerindeki etkilerini tanımlanmasıdır.

Yetkilendirme; Düzenleyici kurumlar radyoaktif maddelerin kullanımını yetkilendirmekten sorumludur. Bu yetkilendirme, düzenleyici kurum faaliyeti desteklemek için gerekli bilgileri inceledikten ve faaliyetin güvenlik ve emniyet açısından gerekli değerlendirmesini yaptıktan sonra verilir.

Gerekçelendirme; Maruz kalma olasılığını değiştirebilecek yeni bir radyasyon kaynağının tanıtımı, cihazın bulundurulmasının ve kullanılmasının zararlarının bireysel ve toplumsal faydalar tarafından ağır bastığından emin olmak gerekir. Sorulması gereken gerçekten brakiterapi uygulamasına ihtiyaç var mı? Kesinse uygulamaya izin verilir.

Radyasyon koruması ve optimizasyonu; Hastaya verilen dozun protokoller ve çalışmalar doğrultusunda kesin olması ve kritik organlar için doz sınırlayıcı kriterler tanımlanmış olarak tedavi için yeterli olmalıdır. Planlama ve uygulama sırasında doz sınırlamalarına dikkat ederek, ihtiyaç duyulan radyasyon miktarı aşılmamalıdır.

Doz kısıtlamaları; mesleki ve kamusal maruziyeti kontrol etmek için kullanılır. HDR brakiterapi uygulamalarında, halkın maruz kalma ihtimali olan dozların optimizasyonu bu kısıtlamaların başında gelmektedir.

Diğer bir kısıtlamada çalışan personelin maruziyetinin engellenmesidir. Radyasyon sızıntısının olmadığı özel proteksiyonlu odalarda, tümörlü bölgeye uygun aplikatör yerleştirmeden sonra radyasyon onkoloğu, tıbbi radyasyon fizikçisi, radyoterapi teknisyeni ve eğitimli brakiterapi hemşiresinin tedavi öncesinde odadan ayrılması ile ve tedavinin dışarıdan kontrol konsolları ile birlikte kullanılan kameralar aracılığıyla yapılması personelin radyasyona maruziyetini kısıtlayıcı yaptırımlardandır.

Tedavi gören hastalar için doz kısıtlamaları yoktur. Dozlar Radyasyon Onkologları tarafından kritik çevre organ dozları da göz önünde bulundurularak protokoller çerçevesinde tanımlanır.

c) Emniyet

HDR brakiterapi kaynaklarının aktiviteleri yüksek olduğundan, güvenlik, hırsızlık, sabotajın önlenmesi, tespiti ve bunlara müdahale edilmesi, yetkisiz erişim, yasadışı transfer veya radyoaktif materyalleri içeren diğer kötü niyetli eylemler emniyeti kapsamındadır (30-32) . Alınması gereken güvenlik önlemleri, kaynağın ait olduğu IAEA tanımladığı kaynak kategorisine bağlı olarak tanımlanır (33). Bu kategoriye göre, radyoaktif kaynakların güvenliğini sağlamak için bir dizi güvenlik önlemlerinin alınması ve tanımlanması gerekmektedir. Bunlar;

- Hırsızlık veya kötüye kullanım riskini en aza indirecek önlemler.

- Radyoaktif kaynağın denetimi, şahsen veya elektronik ortamda kişisel denetim uygulayacak kişilere lisans sahibi tarafından yetki verildiğinde uygulanır.

- Radyoaktif bir kaynak kişisel gözetim altında değilse, elektronik güvenlik önlemleri alınarak herhangi bir hırsızlık veya kötüye kullanma girişimi takip edilmelidir.

- Bir alarm durumunda hırsızlık veya kötüye kullanım tespit edilirse, yetkili makama bildirmek zorunludur.

Kısaca lisans sahibinin, kaynağın nasıl korunacağına ilişkin açıklamayı da içeren bir güvenlik planına sahip olması gerekir

1) Ir-192 Kaynağının Kaydı

Kayıt tutma işlemi sırasında aşağıdaki prosedürün izlenmesi gerekmektedir.

- Yüksek aktiviteli bir kaynak bulunduğu konumdan başka bir kişiye veya transfer edilecekse yapılacak herhangi bir transfer yetkili makama bildirilmelidir.

- Alınan kaynağın ve kullanılmayan kaynağın kaynak verilerinin yetkili makama bildirilmesi için bütün birimin aynı standartlaştırılmış formları kullanması gerekir.

- Yüksek aktiviteli kaynak kullanılmıyorsa, kaynağın bulunduğu merkez, kaynağı güvenli bir şekilde bertaraf etmekle (ya depolanmak üzere IAEA'nın bünyesindeki yerel kuruma veya kaynağın alındığı ülke veya santrala yollamak şeklinde) yükümlüdür.

2) Kaynakların Güvenli Kullanımı

Brakiterapide kullanılan cihazların kullanımı ve KG 'sine ilişkin sorumluluklar;

- Tıbbi cihaz kullanıcılarının ve teknik personelin eğitimi ve sertifikasyonu
- Bu tıbbi cihazların bakımının yapılması
- Tıbbi cihazların kayıt altına alınması ve bakım durumunun genel görünümü,
- Tekrar kullanılabilir tıbbi cihazların temizlenmesi/sterilizasyonu
- Tıbbi cihazları içeren olayların kaydı
- Tıbbi cihazların devre dışı bırakılması

şeklinde özetlenebilir.

3) Personel Eğitimi

HDR programında yer alan klinik personel arasında yetkili kullanıcı hekimi, yetkili tıbbi fizikçi, radyasyon güvenliği görevlisi, dozimetrist, hemşire ve radyoterapi teknisyeni bulunur. Bu rollerden bazıları birleştirilebilir. Örneğin, tıbbi fizikçi aynı zamanda radyasyon güvenliği görevlisi olarak da görev yapabilir ve bir dozimetrist yerine tedavi planlamasını yapabilir. Yetkili hekim ve tıbbi fizikçi, ilgili tıbbi uzmanlık kurulu tarafından sertifikalandırılmalı ve brakiterapi konusunda özel eğitim almış olmalıdır. En önemli husus, HDR tedavilerine katılan tüm personelin aldığı radyasyon güvenliği eğitimidir. Bu eğitim yeni personele ve ardından HDR programındaki herkese yıllık olarak verilmelidir. Bu eğitimlere, tedavi tamamlandıktan sonra veya elektrik kesintisi olduğunda kaynağın yükleyici kasasına geri çekilememesi gibi büyük bir acil duruma uygun müdahale konusunda eğitim de dahildir.

3. Sonuç

Yıllar içerisinde Brakiterapi, bakım standartları olarak 4D görüntüleme ve sofistike planlama yöntemlerini içeren yüksek teknolojili bir radyoterapi modalitesine dönüşmüştür. Bununla birlikte, klinik BT belirsizlikleri yeterince ele alınmamıştır. Bu belirsizliklerin başında kaynak aktivitesinin doğruluğu ve radyoaktif kaynağın optimum kullanımı için kaynak kalite programlarının uygulanmasının ele alınması gerekir. Bu programların mevcut BT cihazın yapısına uygun, merkezde mevcut olan ekipmanlar doğrultusunda yapılması gerekir (34). Günlük nokta kontrolü, uygun ekipmanın (çıkarma kiti ve kurşun konteynır) yerinde olduğundan ve basit acil durum talimatlarının kolayca erişilebilir olacak şekilde asılması gerekmektedir. Herhangi bir şekilde kaynak mekanizmasındaki sorun nedeni ile kaynağın elle geri çekilmesi gerekiyorsa, radyasyon güvenliğinin standart ilkeleri, yani zaman, mesafe ve koruma izlenmelidir. Brakiterapi ekibimizin her bir üyesinin çeşitli acil durumlarda neler yapacağını yıllık eğitim sırasında gözden geçirmesi gerekmektedir. Ayrıca hataların incelenmesi, çoğunun insan hatasından kaynaklandığını göstermektedir

KAYNAKLAR

1. IAEA Human Health Series No.30. Implementation of High Dose Rate Brachytherapy in Limited Resource Settings. Vienna: International Atomic Energy Agency; 2015.

2. American Association of Physicists in Medicine. Code of practice for brachytherapy physics: Report of the AAPM Radiation Therapy Committee Task Group No. 56. Med Phys. 1997;24(10):1557–98.
3. Gerbaulet A, Pötter R, Mazeron JJ, Meertens H, Limbergen EV, editors. The GEC ESTRO Handbook of Brachytherapy. Leuven, Belgium: European Society for Therapeutic Radiology and Oncology; 2002.
4. Supe SS, Ganesh KM, Vaithianathan H, Sankar BN. Radiobiological quality of high dose rate interstitial brachytherapy treatments of carcinoma of the cervix. Rep Pract Oncol Radiother. 2006;11(1):13–22.
5. Kishan A, Cook R, Ciezki J, et al. Radical prostatectomy, external beam radiotherapy, or external beam radiotherapy with brachytherapy boost and disease progression and mortality in patients with Gleason score 9-10 prostate cancer. JAMA. 2018;319(9):896–905.
6. Zaider M, Hanin L. Tumor control probability in radiation treatment. Med Phys. 2011;38(2):574–83.
7. Kutcher GJ, Burman C. Calculation of complication probability factors for non-uniform normal tissue irradiation: the effective volume method. Int J Radiat Oncol Biol Phys. 1989;16(6):1623–30.
8. Jones D. ICRU Report 50—prescribing, recording and reporting photon beam therapy. Med Phys. 1994;21:833–4.
9. International Commission on Radiation Units and Measurements. ICRU Report 62. Prescribing, recording, and reporting photon beam therapy (Supplement to ICRU Report 50). Bethesda, MD: ICRU; 1999.
10. Pieters BR, De Back DZ, Koning CC, Zwinderman AH. Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: A systematic review. Radiother Oncol. 2009;93(2):168–73.
11. International Commission on Radiation Units and Measurements. ICRU Report 38. Dose and volume specification for reporting intracavitary therapy in gynecology. Bethesda, MD: ICRU; 1985.
12. Saynak M, Çukurçayır F, Arlı A, Okumuş D. Yüksek Doz Hızlı Brakiterapi Radyobiyolojisi. Turk J Oncol. 2017;32(Suppl 1):11–22.
13. Kubo HD, Glasgow GP, Pethel TD, Thomadsen BR, Williamson JF. High dose-rate brachytherapy treatment delivery: Report of the AAPM Radiation Therapy Committee Task Group No. 59. Med Phys. 1998;25:375–403.
14. Kutcher GJ, Coia L, Gillin M, et al. Comprehensive QA for radiation oncology: Report of AAPM Radiation Therapy Committee Task Group 40. Med Phys. 1994;21:581–618.
15. Gerbaulet A, Pötter R, Mazeron JJ, Meertens H, Limbergen EV, editors. The GEC ESTRO Handbook of Brachytherapy. Leuven, Belgium: European Society for Therapeutic Radiology and Oncology; 2002. OCLC 52988578.
16. Edai BY. Radiation therapy techniques in cancer treatment. In: Post TW, editor. UpToDate. Waltham, MA: UpToDate; 2022. p. 1–15. Available from: https://www.uptodate.com/contents/radiation-therapy-techniques-in-cancer-treatment?search=radiotherapy&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
17. Venselaar JLM, Pérez-Calatayud J. A Practical Guide to Quality Control of Brachytherapy Equipment. European Guidelines for Quality Assurance in Radiotherapy; 2004. Available from: http://www.estro.org/binaries/content/assets/estro/school/ publications/booklet-8---a-practicalguide-to-quality-control-of-brachytherapy-equipment.pdf
18. Thomadsen BR, Erickson BA, Eifel PJ, Hsu IC, Patel RR, Petereit DG, et al. A review of safety, quality management, and practice guidelines for high-dose-rate brachytherapy: Executive summary. Pract Radiat Oncol. 2014;4(2):65–70.
19. Nath R, Anderson LL, Meli JA, Olch AJ, Stitt JA, Williamson JF. Code of practice for brachytherapy physics: Report of the AAPM Radiation Therapy Committee Task Group No. 56. Med Phys. 1997;24(10):1557–98.
20. International Atomic Energy Agency. Setting Up a Radiotherapy Programme: Clinical, Medical Physics, Radiation Protection and Safety Aspects. Vienna: IAEA; 2008.
21. Ballester F, Puchades V, Lluch JL, Serrano-Andrés MA, Limami Y, Pérez-Calatayud J, et al. Technical note: Monte-Carlo dosimetry of the HDR 12i and plus 192Ir sources. Med Phys. 2001;28(12):2586–91.
22. International Atomic Energy Agency TECDOC-1274. Calibration of Photon and Beta Ray Sources Used in Brachytherapy. Vienna: IAEA; 2002. ISSN 1011-4289.
23. International Commission on Radiation Units and Measurements. ICRU Report 58. Dose and Volume Specification for Reporting Interstitial Therapy. Bethesda, MD: ICRU; 1997.
24. Commissie N, Stralingsdosimetrie V. Code of Practice for Quality Assurance of Brachytherapy with Ir-192 Afterloaders Disclaimer regarding NCS reports. 2018 May.
25. International Atomic Energy Agency Tec Doc1079. Calibration of Brachytherapy Sources: Guidelines on Standardized Procedures for the Calibration of Brachytherapy Sources at Secondary Standard Dosimetry Laboratories (SSDLs) and Hospitals. Vienna: IAEA; 1999.
26. Bidmead AM, Sander T, Locks SM, Lee CD, Aird EGA, Nutbrown RF, et al. The IPEM code of practice for determination of the reference air kerma rate for HDR 192Ir brachytherapy sources based on

the NPL air kerma standard. Phys Med Biol. 2010;55(11):3145–59. doi:10.1088/0031-9155/55/11/011.
27. Hanson WF. Calibration of brachytherapy sources. Int J Radiat Oncol. 1979;5(April):114–5.
28. Küçük H. Brakiterapi sistemlerinde kalite kontrol. In: Becerir H, editor. Radyoterapi Fiziği. 1st ed. İstanbul: Nobel Akademik Yayıncılık; 2020. p. 921–31.
29. Allisy A, Jennings WA, Kellerer AM, Müller JW, Rossi HH, Seltzer SM. ICRP-60. Fundamental quantities and units for ionizing radiation. Int J Radiat Oncol. 1998;31(1):1–31.
30. International Atomic Energy Agency. Terminology Used in Nuclear Safety and Radiation Protection. Vienna: IAEA; 2007. Available from: http://www-ns.iaea.org/standards/
31. International Atomic Energy Agency. Code of Conduct on the Safety and Security of Radioactive Sources. Vienna: IAEA; 2004.
32. Of C, On C, Safety THE, Of S, Sources R, Sur CDEC, et al. Code of Conduct on the Safety and Security of Radioactive Sources.IAEA.2004 https://www.osti.gov/etdeweb/servlets/purl/20485104
33. International Atomic Energy Agency. Safety Standards for Protecting People and the Environment: GSR Part 3. Vienna: IAEA; 2014. Available from: http://ec.europa.eu/dgs/communication/services/visual_identity/index_en.htm
34. Wilkinson DA. High dose rate (HDR) brachytherapy quality assurance: A practical guide. Biomed Imaging Interv J. 2006;2(2).